1957

Probenecid : with particular reference to its use as an adjunct in penicillin therapy

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PROBENECID, WITH PARTICULAR REFERENCE TO ITS USE AS AN ADJUNCT IN PENICILLIN THERAPY

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Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1957

Omaha, Nebraska

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I. History and Chemistry

Probenecid was developed as part of a specific pharmacologic study to find agents that would inhibit the rapid renal tubular excretion of penicillin. It was synthesized by Miller, Ziegler and Sprague[1] and studied by Beyer and his associates of the pharmacology section of Merck, Sharp and Dohme Inc. in 1949 as part of a systematic study to find an organic acid that would depress the renal tubular excretion of penicillin.

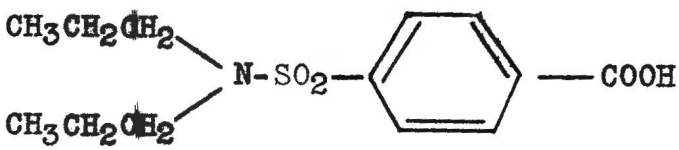
Rammelkamp and Keefer[2] (1943) showed that 58 per cent of aqueous penicillin administered by the intravenous route was excreted by the kidneys largely during the first hour after injection. Approximately 60 to 90 per cent of an intramuscular dose of penicillin in aqueous solution is eliminated in the urine largely within an hour after injection.[3] About 20 per cent of penicillin is excreted by glomerular filtration and 80 per cent by tubular excretion.[4] This large renal tubular excretion of penicillin is the basis of the usefulness of probenecid in penicillin therapy as will be noted in the discussion of the pharmacology of probenecid ('Benemid').

It was noted (Rammelkamp, 1943)[5] that Diodrast

given intravenously decreased the excretion of penicillin and that there was a mutual depression of the renal clearances of Diodrast and phenol red when these substances were given simultaneously. It was postulated that there may be a competition for elimination through a common renal tubular mechanism to account for these inhibitory phenomena. Para-aminohippurate in large amounts by intravenous infusion also was found to inhibit renal excretion of penicillin.

Carinamide (4'-carboxyphenylmethane sulfonanilide) was the first tubular blocking agent to receive clinical trial. It was found to be an effective agent by the oral route but required large and frequent doses in the range of 18 to 24 grams a day because of its fairly rapid tubular excretion.[6] Benemid, which probably acts on the same enzymatic systems in renal secretory function as carinamide, overcomes this difficulty because of its slow elimination from the body.

Probenecid is a benzoic acid derivative with the following structural formula.



p-(di-n-propylsulfamyl) benzoic acid

Various congeners of probenecid have been studied

and compounds of higher molecular weight by increasing the size of the N-alkyl substitution are more effecient blockers of renal tubular transport in that they are not themselves excreted into the urine.[4] However, this fact accounts for their greater toxicity and the N-dipropyl derivative, probenecid, appears to have the safe optimal activity.

Probenecid is a white crystalline powder, nearly insoluble in water and practically tasteless.[7]

II. Pharmacology

The principle pharmacologic actions of probenecid are confined to its effects on the renal tubule. Of practical importance are its effects on the renal excretion of the penicillins, uric acid and para-aminosalicylic acid (PAS).

Beyer and his associates reported in 1951[8] that probenecid "selectively and reversibly inhibits the transport mechanism responsible for the tubular secretion of the penicillins, p-aminohippurate and phenol red". They found that it did not inhibit all tubular secretory systems since it has no effect on the renal elimination of N'-methylnicotinamide and did not affect the glomerular filtration rate or reabsorption of glucose, arginine, urea, sulfonamides, sodium, potassium, chlorides or

or phosphates. The compound increased the excretion of uric acid by the ordinary dog but inhibited the more rapid elimination of uric acid by the 'Dalmation'.

It has been reported that probenecid inhibits the reabsorption of phosphate by the renal tubules and has been used in familial nephrogenic osteopathy and to control the tetany of hypoparathyroidism.[10] Probenecid has an enhancement effect on plasma concentrations of pantothenic acid given orally or parenterally and a slight enhancement effect upon the plasma concentrations of the sulfapyrimidines. Probenecid does not increase the plasma concentrations of streptomycin, chlortetracycline, oxytetracycline, chloramphenicol or neomycin.[10] It has been claimed recently that probenecid influences sodium and water excretion in cardiac patients.

Estimation of Benemid levels in body fluids was done by two analytic methods described by Tillson and associates in 1950.[9] The first method depends on the fact that the compound can be extracted in chloroform from an acidic, aqueous medium and in turn reextracted from chloroform in 0.1 N sodium hydroxide. The alkaline solution is examined spectrophotometrically at a wave length of 242.5 millimicrons. In the second method, the drug is extracted into chloroform from an acidic aqueous medium and the chloroform layer shaken with an aqueous solution of methylene blue. The colored salt,

formed at the surface, is soluble in the solvent making it possible to determine the amount present by examining the chloroform layer colorimetrically.

Benemid is absorbed rapidly following its oral administration to laboratory animals and to man.[11] Following a single oral dose of the drug, a determinable and functionally useful plasma concentration persists in the dog for over 44 hours. In man, measurable concentrations of probenecid are observed in the plasma within a half-hour after the administration of as little as 0.5 grams.[6] Peak plasma concentrations are reached about two hours after a single oral dose.[4] The compound per se is excreted so slowly that its renal clearance cannot be estimated, since little or none of the drug is found in the urine. It is eliminated almost entirely by glomerular filtration so that signigicant plasma concentrations of the drug are observed as long as 24 hours after the oral administration of a single one gram dose.[6] A patient with normal renal function ingesting a two gram dose per day, administered as one gram every 12 hours or as 0.5 gram every 6 hours, will show continuing plasma concentrations in the range of 4 milligrams per 100 milliliters.[10]

Probenecid is partially bound to plasma proteins and the unbound portion gains access to the glomerular

filtrate but is largely reabsorbed by the renal tubule.[4] Little of the compound is secreted by the tubules so that little free probenecid is found in the urine. It is slowly conjugated with glycuronic acid and excreted in this form. McKinney and others[12] found a non-fermentable reducing substance in the urine of dogs on oral Benemid that was in part glucuronic acid. The metabolic product in the urine is split by hydrolysis when heated, thereby releasing Benemid per se, and glucuronic acid which is a reducing substance.

The exact mechanism of action of probenecid as a competitive inhibitor of the renal secretion of organic acids is unknown. Beyer et al in 1950 demonstrated that probenecid inhibits the enzyme or enzyme systems involved in the conjugation of glycine with para-aminobenzoic acid.[1] Benemid did not inhibit glucose phosphorylation by phosphorylase in the presence of adenosintriphosphatase and thus did not decrease the availability of energy derived from the phosphate cycle, which is a coupled component of the conjugative reaction.

The conjugation of benzoic acid and related compounds occurs in two steps and involves coenzyme A (Schachter and Taggart, 1953, 1954).[4]

1.) Benzoate + CoA + ATP $\rightleftharpoons$ Benzoyl-CoA + adenylic + pyrophosphate
(activated benzoate)

2.) Benzoyl-CoA + glycine $\rightarrow$ hippurate + CoA

Probenecid has been found to compete effectively with benzoate in the activation reaction. It exhibits no effect on the subsequent transfer to glycine.

The exact relationship of these reactions to the renal transport of organic acids has not been demonstrated. It may be postulated that the intermediate compound in the renal transport of penicillin and related compounds is the CoA complex and that probenecid interferes with transport by forming a complex with CoA that is less dissociable than that of penicillin.

III. Animal Studies

Verwey and his associates[13] compared the effects of probenecid and carinamide on the penicillin therapy of experimental pneumococcic infections in mice. They used 16 to 22 gram female mice and infected them intraperitoneally with about 1000 MLD of a Type I pneumococcus contained in 0.5 ml. of a diluted 6 hour broth culture. Intramuscular sodium penicillin, 0.05 ml., was given at zero hours and at 12 hours after infection. Five to 10 mg. of probenecid or carinamide was suspended in 0.5 ml. of 0.5 per cent gum tragacanth and given by stomach tube at zero hour or at 1, 2, 4, 6, 8 or 10 hours before each penicillin injection. The infected control mice receiving penicillin but no adjunct therapy were fed 0.5

ml. of tragacanth material at zero hour. Each treatment group consisted of ten mice and the experiment was terminated seven days after infection. The dose of penicillin protecting 50 per cent of mice (PD 50) was calculated for each treatment schedule, using the method of Reed and Muench (Am. J. Hyg. 27: 493, 1938). The results of the experiments were expressed as the per cent reduction in the dose of penicillin protecting 50 per cent of animals (PD_{50}) compared to the control values obtained when no adjunct therapy was given. The data from several separate experiments were averaged and the effect of the adjunct pre-feeding times on the penicillin PD_{50} was tabulated.

The mouse protection data showed clearly that the effect of probenecid on penicillin activity was considerably longer than the effect of carinamide. They concluded that the prolonged effectiveness of probenecid in mice is the result not only of slower elimination but also of greater intrinsic activity. Although the renal clearance studies of Beyer et al have indicated equal plasma concentrations of carinamide and probenecid exert approximately equal effects on penicillin excretion in dogs, their data indicated that, in the mouse, probenecid may be at least twice as effective as is carinamide at apparently equivalent plasma concentrations. This seeming discrep-

ancy in the two types of experiments may be explainable on the basis of species differences in the metabolism of these two compounds. Clinical impressions, based on plasma levels of these two drugs necessary to produce enhanced penicillemia in man, suggest that the greater effectiveness of probenecid demonstrated in mice is also found in man.

They concluded that the oral administration of either carinamide or probenecid enhances the therapeutic effectiveness of intramuscular penicillin in mice experimentally infected with Type I pneumococcus and that in equal oral doses, probenecid has 2 to 3 times the duration of action of carinamide. Based on protection test data, probenecid has about two times the intrinsic activity of carinamide. The prolonged effectiveness of probenecid in mice is the result of this greater intrinsic activity and of its slower disappearance from the blood stream.

Miller and Verwey[14] studied the effect of probenecid on combined penicillin and triple sulfonamide therapy of experimental streptococcal infections in mice. Using much the same methods of the study described above, they observed that when a constant level of 0.5 mg. of triple sulfonamide was incorporated into the therapeutic dose, the amount of penicillin required to

protect 50 per cent of the mice (PD_{50}) was reduced from 124 to 50 units. Neither 50 units of penicillin nor 0.5 mg. of triple sulfa alone protected any mice. The addition of 10 mg. of probenecid to the penicillin therapy reduced the PD_{50} to 40 units.of penicillin and the combination of 10 mg. Benemid, 0.5 mg. triple sulfa and penicillin reduced the PD_{50} to 20 units. Neither probenecid nor probenecid plus 0.5 mg. triple sulfa protected any mice. They concluded that penicillin and sulfonamides are truly synergistic in their action and that the addition of probenecid to such a mixture results in therapy more effective than that of either probenecid and penicillin or sulfonamides and penicillin.

IV. Clinical Studies

Boger and his associates[6] in 1950 were among the first to report on the clinical use of probenecid in p-amino salicylic acid and penicillin therapy. On the basis of animal studies, a safe dose of between one and four grams per day was decided for people. Single oral doses of 0.5 to 1 gram given cautiously were found safe and it was found that as much as four grams could be given without gastro-intestinal irritation or systemic symptoms. In dogs, it had been demonstrated that as

little as 6 mg. per kilogram of body weight resulted in almost complete suppression of renal tubular excretion of penicillin and that larger doses of the drug did not produce any further decrease in the renal clearance of penicillin. Thus, it was anticipated that one to two grams of probenecid might produce a pharmacologic effect in man and the effect on penicillemia from intravenous, intramuscular, and oral penicillin was noted.

They studied 37 patients with probenecid and intravenous, intramuscular, and oral crystalline and procaine penicillin. Their study showed that Benemid is capable of increasing by two to four times the plasma concentrations of penicillin and para-amino salicylic acid. Due to rapid gastro-intestinal absorption, pharmacologically effective plasma concentrations are attained within two hours after oral administration. The drug is slowly excreted so that following a one or two gram oral dose of Benemid, an effect on the plasma concentration of penicillin and PAS can be observed for periods up to 8 hours and detectable plasma concentrations of the drug are maintained following single doses for as long as 12 hours. The repeated administration of 0.5 to 1 gram of Benemid every six hours maintains a plasma concentration of the drug from 2 to 10 mg. per 100 ml. of plasma and this range of concentration appears pharmacologically

effective in retarding the rate of elimination of both penicillin and PAS. These findings in man are in good agreement with the effective plasma concentrations that have been observed in dogs -- 3to 6 mg. per 100 ml. of plasma.

By comparison of carinamide and Benemid in people, they found that 2 grams per day of Benemid produces an effect on the excretion of penicillin and PAS equivalent to that produced by 24 grams of carinamide per day.

They report also that probenecid has no effect on the excretion of streptomycin, aureomycin, oxytetracycline, or chloromycetin.

Waldo et al[15] tested fifteen patients with Benemid and found that in small doses the drug enhances penicillemia and gives no evidence of toxicity. Its full effect with repeated 0.5 gram doses is often achieved on the second day rather than the first, as is the case with carinamide. Giving a higher initial dose of Benemid results in earlier increase of the penicillemia.

Meads et al [16] studied probenecid in 27 healthy subjects and one patient with subacute bacterial endocarditis. They concluded that two grams of Benemid daily (one gram every twelve hours) increased penicillemia two times or more and 3 grams daily (one gram three times a day) increased the penicillemia five times or more.

In their paper, Boger reported that in 12 cases of so-called penicillin-resistant cases of subacute bacterial endocarditis with the use of probenecid penicillemia of 40 to 100 units per milliliter was achieved in all cases and that this treatment was effective in curing the disease.

Burnell and Kirby[17] studied the effect of 0.5 gram oral doses of probencid every 6 hours on penicillemia in 74 patients. They point out that there is a great variability in penicillin levels from patient to patient. In 51 patients treated with procaine penicillin, there was enhancement of penicillemia following Benemid in 81 per cent of instances with an average fold increase of 2.87. In 23 patients treated with crystalline penicillin, the levels were higher in 96 per cent of cases with an average fold increase of 5.10.

With probenecid, they could show penicillin blood levels of 40 to 80 units per milliliter with the same large amounts of penicillin used to produce levels of 20 units per ml. using penicillin alone. A 0.5 gram dose of Benemid every 6 hours in addition to a million units crystalline penicillin intramuscularly every two hours gave penicillin blood levels never lower than 40 units per milliliter.

They treated four patients with staphylococcal

meningitis with Benemid and intramuscular penicillin and got an elevation of spinal fluid penicillin levels of ten to forty times that achieved with penicillin alone. The clinical response in these patients was very good after this treatment.

Baker and Pilkington[18] reported a case of Streptococcal faecalis endocarditis that did not respond to large and long-continued dosage with penicillin, streptomycin, aureomycin and chloramphenicol. The causal streptococcus was sensitive in vitro to aureomycin and chloramphenicol, but these antibiotics did not eradicate the infection. The streptococcus was relatively insensitive to penicillin, but the very high penicillemia achieved with the aid of probenecid was sufficient to arrest the disease permanently. The patient was given four million units of aqueous penicillin intramuscularly every 3 hours and Benemid one gram every 6 hours for 59 days. The penicillemia was tested at one, two and three hours after injection on several occasions and found to range from 128 to 32 units per ml. of plasma. There were no toxic effects except slight abdominal discomfort. The outcome of this case is consistent with the view that penicillin is bactericidal, whereas the other antibiotics used are only bacteriostatic.

Douthwaite[19] reported the successful treatment of a

case of staphylococcal septicemia with Benemid and penicillin after "heroic" doses of the latter and full doses of aureomycin and other broad-spectrum antibiotics had failed.

Similarly, he attributed the successful treatment of two cases of resistant Streptococcus viridans endocarditis to the combination of penicillin and probenecid.

Loewe et al,[20] reporting on treatment programs for refractory cases of subacute bacterial endocarditis, recommend a daily dose of 1.8 to 2 million units of procaine penicillin intramuscularly (divided in two doses) for four weeks. "Our daily dose plan of two million units of penicillin is predicated on in vitro sensitivity studies of the infecting organisms recovered from our patients with subacute bacterial endocarditis (SBE). The bactericidal in vitro sensitivity value of 157 infecting organisms was two Oxford units or less per milliliter of test broth. Therefore, the therapeutic blood level of penicillin should be at least two Oxford units per milliliter of blood which is uniformly achievable by the conjoined use of two million units of penicillin intramuscularly plus probenecid orally." They used 0.5 gram probenecid every 6 hours around the clock for enhancing purposes and to maintain measurable effective penicillin levels throughout all or most of the treatment period.

The expected theoretical blood level of penicillin

after a given dose can be consistently assured when probenecid is used with the penicillin. "This agent has been so useful in affording predictable requisite penicillin blood levels, and we have come to rely upon it so much that we now incorporate the drug routinely in our treatment program."

Of academic interest is the use of penicillin and probenecid in the treatment of typhoid carriers. Some cases of chloramphenicol-treated typhoid fever are not bacteriologically controlled and relapse has been seen within two weeks after cessation of treatment regarded as adequate.[21] Also it is acknowledged that chloramphenicol is not effective in treating the carrier state.

Boger et al[21] reported a case of typhoid fever successfully treated with penicillin and suggest that previous failures to successfully treat typhoid fever with penicillin were due to inadequate penicillemia to inhibit the infecting organisms. Evans has shown that 10 units of penicillin per milliliter of plasma are necessary to inhibit a majority of strains of S. typhosa and has established that in adequate concentrations (about 25 units per ml.) penicillin is capable of killing S. typhosa. (Evans, J. W., Penicillin sensitivity of B. typhosum, Lancet 2:113, 1946)

Therapy was started early in this illness and

aqueous sodium penicillin one million units I.M. every 3 hours and Benemid 0.5 gram every 6 hours were given so that a penicillemia of greater than 10 units per ml. was maintained at all times during the 15 days of therapy. At the end of treatment, the patient had negative blood, stool and urine cultures on three successive occasions.

While giving sodium penicillin I.M. one million units every 3 hours alone, the penicillemia ranged from 8.1 units per ml. one hour after injection to 2.7 units per ml. three hours after injection. When the same dose of penicillin was given in conjunction with two grams per day of Benemid by mouth in divided doses, the penicillemia on two occasions was 66 units and 58 units per milliliter of plasma at one hour and 21 and 34 units per ml. at three hours. Thus when penicillin alone was administered, at no time, or only briefly during the first hour after injection, were concentrations inhibitory for S. typhosa obtained in the blood stream. In contrast, inhibitory levels were attained and maintained continuously when the same dose of penicillin was given with Benemid.

Parker et al[22] treated six typhoid carriers of long standing with three million units of penicillin every 6 hours and 1.5 grams of Benemid two times a day for 10 days. One of the six carriers shed typhoid

organisms in the stool 28 days after the treatment was stopped and another carrier was unaffected thoughout the course of treatment and observation. Of the other four, two had been observed four and five months respectively and had not shed the pathogens. Two other patients under observation for a short period had remained free of S. typhosa. Because of the variability of the typhoid carrier state and preliminary nature of their study they concluded no definite conclusions could be made and the the method of treatment needed further evaluation.

Frisk et al[23] in a study of probenecid and oral penicillin concluded to their satisfaction that the oral administration of probenecid and penicillin caused a significant elevation of penicillemia compared to levels attained with comparable oral doses of penicillin alone, even with a probenecid dose of only 0.25 gram. Within the dosage range of probenecid used (0.25 to 1.0 gram) there was a close and linear relationship between the amount of probenecid given and the serum penicillin level attained.

When repeated oral doses of penicillin and probenecid are administered, a therapeutically effective penicillemia could easily be maintained with a rather small dose of penicillin. Thus a dosage scheme of 500,000 units of potassium penicillin and 1.0 gram of probenecid

every 8 hours, on the average, ensured a minimum penicillemia of 0.1 units per ml. With probenecid oral penicillin therapy it is possible to achieve results with smaller doses of penicillin and with doses given at longer intervals. Their results indicate that an oral dose of 500,000 units penicillin and 1.0 gram of probenecid every 12 hours would suffice for the treatment of the majority of infections caused by penicillin-sensitive organisms.

In a study of six healthy patients using each subject as his own control, Boger et al[24] showed that oral penicillin in conjunction with probenecid was equivalent, on the basis of penicillin plasma concentrations, to intramuscularly administered procaine penicillin. An initial oral dose of 400,000 units of potassium penicillin G in combination with one gram of Benemid results in a peak concentration of one to two units per ml. Subsequent doses of 300,000 units of penicillin in combination with 0.75 gram of Benemid at eight hourly intervals result in peaks approximating one unit per ml. and the penicillemia, maintained over a 24 hour period, was 0.05 unit per ml. or above. A plasma concentration of greater than 0.03 unit per ml. is popularly recognized as a therapeutically effective plasma penicillin level, although penicillemia is not a complete assessement of the

therapeutic potential of a given dose. The total oral dose for a day was one million units. The levels attained here, on a 24 hour basis, compare favorably with those attained with a single intramuscular injection of 300,000 units of procaine penicillin in aqueous suspension. Boger concludes, "Benemid confers upon orally administered penicillin the same property of prolonged high penicillin plasma concentrations as the discovery of insoluble procaine penicillin did for intramuscularly administered penicillin."

In an evaluation of oral penicillin therapy Boger[25] points out that it has been shown that probenecid has a two to ten fold enhancement effect upon the penicillemia resulting from the intramuscular administration of potassium and procaine penicillin, on the hydriodide of the diethylaminoethyl ester of penicillin G, on benzethacil, on penicillin O and on benethamine. Benemid appears to enhance the penicillemia with penicillin V according to the work of Martin et al[26].

Boger[25] in his studies on oral penicillins (1954) concluded that water-soluble potassium penicillin G, administered in conjunction with probenecid, furnishes higher and more prolonged penicillin plasma concentrations than those observed following the administration of any other available oral penicillin dosage form. He states

that the oral administration of penicillin may be the safest route of administration but urges that oral penicillin not be used in the treatment of fulminating infections, as meningitis or osteomyelitis, nor in the therapy of subacute bacterial endocarditis.

V. Toxicology, Side Effects and Doses

McKinney et al[12] studied the acute and chronic toxicity of probenecid in mice, rats, rabbits and guinea pigs. The acute toxicity signs were thought to be of central nervous system origin with deaths apparently due to respiratory arrest during tonic convulsions. The values of the LD_{50} in the different animals when probenecid was given by the intravenous, subcutaneous, intraperitoneal or oral routes indicate that the drug was well absorbed by all routes and that the toxicity for the different species of animals was similar.

Daily oral administration of probenecid to six dogs for eight weeks in doses as high as 200 mg. per kilogram and to 56 rats for 12 weeks as high as 400 mg. per kilogram did not cause changes in hematologic values that could be attributed directly to the drug. Chemical studies of the plasma and the urine of the dogs did not reveal significant changes from the control values.

Drug sensitivity tests in guinea pigs failed to produce local or generalized reactions to probenecid.

Boger and Strickland[10] in a review of 2,502 patients indicate that in a daily dose of two grams of probenecid the drug can be safely administered for periods up to four years at the time they did their study. The most common manifestation of intolerance is gastrointestinal symptoms, occuring in 3.1 per cent of patients studied. These symptoms vary from vague abdominal distress, anorexia, nausea, vomiting, abdominal cramps, and epigastric burning to frank vomiting and diarrhea. Typical hypersensitivity reactions with chills, fever, rash, myalgia, dyspnea, nausea, vomiting or vasomotor collapse have been observed in eight patients and skin rashes have been observed in 34 patients. It is likely that some of these skin rashes were due to concomittantly administered penicillin.

At the time of this report (1954) no deaths were attributable to probenecid therapy. There is no evidence of aggravation of preexistent renal damage, no hepatic toxicity and no reported case of suppression of the hematopoietic system. A total of 175 side-effects have been noted in a group of 2,502 patients, representing an over-all percentage of 7.94 per cent. Thirty-five of these reported side effects were related to the urinary

tract, where the question may be raised whether the manifestations are truly side-effects and evidences of toxicity or if they are, in fact, evidences of the uricosuric activity of probenecid producing urate calculi. Probenecid has established itself as a drug of low toxicity.

Experience has shown that two grams per day represents the average adult dose which is tolerated. In the therapy of gout, probenecid is used in daily doses varying between 0.5 and 2 grams per day. [10]

In a study of 85 children by Coriell et al[27], they concluded that the optimal oral dose of Benemid was found to be an initial dose of 25 mg. per kilogram of body weight followed by 10 mg. per kilogram every 6 hours for maintenance therapy. For children over 50 kilograms of body weight the adult dose is adequate, 0.5 gram every 6 hours following an initial dose of one to two grams if rapid action is desired.

VI. Discussion

It is generally agreed that "the effective penicillin time in the serum is usually a reasonable approximation of the penicillin time in the tissue fluids".[28] Infections caused by the gonococcus, the pneumococcus, and the spirochete of syphilis can be treated with amounts of penicillin that give only transient penicillemia.

Here the use of probenecid with penicillin would be of no practical value. However, in infections caused by microorganisms resistant to penicillin in commonly employed blood levels or in foci of infection that present a barrier to the ready diffusion of antibiotic, the use of probenecid is indicated in order to achieve higher penicillin plasma concentrations.

It may be argued that his can be accomplished by simply giving more penicillin. However, there is a definite limitation with regard to administering more penicillin by mouth. In children and to a lesser degree in adults, an oral dose of penicillin in excess of two million units per day exerts such a marked antibacterial effect upon the gastrointestinal flora that in some patients loose stools and diarrhea are observed, even as they are noted with chlortetracycline and oxytetracyline.[25] In pediatric practice it has been commonly observed that parents overdose their children with some of the flavorable oral suspensions of penicillin. The enhancement effects of probenecid would appear to have merit in extending the usefulness of penicillin by mouth.

Probenecid is indicated in penicillin therapy where continued high penicillin plasma concentrations are desired over a long period of time. Thus it is of value in the penicillin treatment of subacute bacterial endocarditis,

septicemia, staphylococcal osteomyelitis, some types of meningitis, infections caused by relatively penicillin-resistant organisms, and infections sequestered in tissue of low permeability. Probenecid should improve the therapeutic effectiveness of the penicillin dose given in these cases as well as reduce the cost of treatment where long-term therapy is needed. A reduction in penicillin dosage from one million to 500,000 units a day would not be significant in this respect, but a reduction from 10 million to 5 million units per day in the treatment of SBE, for example, where therapy is long-continued, would represent a considerable reduction in cost of treatment.

In pediatric therapy using oral penicillin, probenecid is beneficial in reducing the amount and frequency with which medication must be taken.

Benemid has established itself as a drug of low toxicity. Since it usually will be prescribed for only about a weeks time in conjunction with most penicillin therapy, the development of side-effects is less likely to occur than when used over long periods of time as in the therapy of chronic gout.

VII. Summary

A brief review of agents known to block the renal tubular transport of penicillin and other organic acids

is given. The chemistry of probenecid, one of the more recent and to date the most effective clinically of these agents, is discussed. The unique pharmacologic action of probenecid as a selective and reversible inhibitor of the renal tubular transport of certain organic substances and a probable mechanism of its action in the renal tubule cell is presented. Its rapid gastro-intestinal absorption and slow renal elimination enable it to exert a measurable enhancement effect on penicillin and PAS levels for as long as eight hours after a single oral dose. Studies of probenecid-penicillin therapy of experimental infections in mice indicate probenecid enhances the therapeutic effectiveness of penicillin. Studies of about 150 patients indicate that probenecid in doses of 0.5 to 2 grams a day enhances penicillin blood levels two to four times. It has been found a valuable adjunct in the penicillin therapy of subacute bacterial endocarditis. It has been used with penicillin in the treatment of typhoid fever. Probenecid has been found valuable in sustaining a significant penicillemia in conjunction with oral penicillin.

Probenecid has established itself as a drug of low toxicity with side effects occurring in only about eight per cent of cases. These are usually mild gastro-intestinal complaints. Effective adult doses are usually 0.5 to 2 grams a day. The recommended pediatric dose is 25 mg. per kilogram initially with 10 mg. per kilogram for

maintenance.

Probenecid is a valuable adjunct to the penicillin therapy of subacute bacterial endocarditis, septicemia, staphylococcal osteomyelitis and infections caused by relatively penicillin-resistant organisms and infections sequestered in tissues of low permeability.

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