Editorial

GENTAMYCIN

Gentamycin an extensively used antibiotic is derived from the fermentation of Micromonospora purpurea. It is water soluble, stable over a wide pH range and relatively heat resistant (Weinstein et al., 1963). Absorption is poor by oral administration whereas intramuscular or intravenous therapy gives adequate serum levels. The drug does not bind itself to plasma proteins (Gordon et al., 1972), and it is given intrathecally to treat meningitis (Kaiser and Mcgee, 1975). In ophthalmology gentamycin has given good results when used topically or by local injection (Records 1976). In obstetrics it has been observed that gentamycin crosses the placental barrier (Weinstein et al., 1976). Gentamycin is not metabolised in the body and is excreted by glomerular filtration (Gyselynck et al., 1971). After a single dose 40% to 65% is recovered in the first twenty four hours. Later almost 90% is recovered (Wilson et al., 1973). The drug accumulates within the kidney tissues and renal cortial concentrations are often many times the plasma levels (Luft and Kleit, 1974; Edwards et al., 1976; Schentag and Jusko, 1977). The serum half life of gentamycin in patients with a normal renal function is two hours. The prolongation of the serum half life is directly proportional to the fall of creatinine clearance.

In patients with a normal creatinine clearance an initial dose of 2 mg/kg body weight followed by 1 to 1.5 mg/kg body weight every eight hours gives adequate serum levels to treat infections. In patients with impaired renal function, the dose has to be adjusted as the main route of excretion is the kidney (Goodman et al., 1975). The alteration is made either in the interval of administration or the dose. A routine dose may be given with the time interval calculated by the formula every eight hour times the serum creatinine concentration. The dose may be altered by the formula 1 to 1.5 mg/kg body weight divided by the serum creatinine concentration given every eight hours. Greater accuracy can be achieved by using serum levels of gentamycin as a guide.

Although the antibacterial spectrum of gentamycin includes both gram positive and gram negative bacteria, the species covered are few. The gram positive include only staphylococcus aureus and staphylococcus epidermidis. The gram negative spectrum has a slightly wider range. Most members of the Enterobacteriaceae and most pseudomonas aeruginosa strain are sensitive to gentamycin. But it has also been established that pseudomonas series other than pseudomonas aeruginosa and all anaerobic bacteria are resistant to gentamycin, the reason being non-transportation of the drug inside the bacterial cell. Synergistic action has been advised by using penicillin and cephalosporin with gentamycin. The mechanism is explained as damage to the cell membrane by penicillin which allows penetration of gentamycin (Moellering et al., 1971). This combination is effective against a wider range of bacteria including streptococci viridans, streptococci faecalis, streptococcus agalactiae and listeria monocytogenes (Deveikis et al., 1977).

The clinical use of gentamycin is mainly limited to infections caused by gram negative Enterobacteriaceae and pseudomonas aeruginosa. It may be used as an exception in gram positive infections in combination with penicillin or ampicillin. But the major role is played in septic states with neutropenia. Such patients do not respond if an aminoglycoside is used alone (Bodey et al., 1972). In urinary tract infections gentamycin is useful as the organisms are usually resistant to other antimicrobial agents. Pulmonary infections with gram negative organisms respond equally well to other aminoglycosides as to gentamycin due to the good host defenses. Various subcutaneous and traumatic wounds where aerobic and anerobic organisms are encountered are treated with success by using gentamycin. Intravitreous injection of gentamycin has been proved to be effective in Keratitis due to pseudomonas and proteins.

The nephrotoxic and ototoxic effects of gentamycin are well recognised. Animal studies in rats showed cloudy swelling and vacuolation of the proximal tubular cells (Black et al., 1963) which progressed to diffuse tubular necrosis (Hsu et al., 1974; Bennett et al., 1976). In humans 2 to 10% of cases show gentamycin toxicity (Hewitt 1974), and it is dose related (Fanning et al., 1976), seen more commonly in old debilitated patients, in patients with previous renal damage and in those with a contracted intravascular volume (Fanning et al., 1976; Gary et al., 1976). Two forms of nephrotoxicity are experienced in gentamycin therapy. A dose related non-oliguric form which proceeds to gradual fall in renal function and oliguria. A prolonged course of therapy often gives a non-oliguric type of renal damage which is milder and follows inadequate monitoring of the renal status (Gary et al., 1976). Mild proteinuria and granular cylindruria occurs initially followed by gradual decline in the glomerular filtration rate. However the changes are reversible if the drug is withdrawn early. The normalisation of the renal function takes from weeks to months. Gentamycin nephrotoxicity has been observed in concomitant therapy with other drugs. Methoxyflurane anaesthetic along with gentamycin increases the risk. The combination of cephalosporin and gentamycin are significant for producing renal toxicity (Just et al., 1977).

The exact mechanism is not clear, but adequate precautions are necessary. A daily monitoring of the renal function and an appropriate dose adjustment reduces the risk.

Ototoxicity was reported in animal experiments showing progressive destruction of vestibular sensory cells. Cochlear damage is less prominent. In man, 2-3% patients develop ototoxicity with a predominate of vestibular damage leading to vertigo, ataxia and nystagmus. Auditory damage is manifested as loss of high tone hearing and tinnitus progressing to total deafness. The injury is usually bilateral but is reversible if therapy is stopped in the early state. Prolonged therapy can cause permanent harm. The cause of ototoxicity is not yet ascertained. It is neither dose related nor does it depend on the duration of therapy. Thus a dose assessment of auditory function especially in prolonged use is important. Other forms of toxicity reported are neuromuscular blockade (Holtzman, 1976; Warner and Sanders, 1971) which can be reversed by administration of calcium. Transient agranulocytosis has also been occasionally seen.

Gentamycin despite its toxicity risks is used widely to treat aerobic gram negative infections. It is important to give attention to serum levels and follow the renal function and eighth nerve function closely, which will give efficacy and reduce the risk of toxicity.

References

Bennett, W.M., Hartnett, M.N., Gilbert, D., Houghton, D. and Porter, G.A. (1976) Effect of sodium intake on gentamycin nephrotoxicity in the rat. Proc. Soc. Exp. Biol. Med., 151:736.

Black, J., Calesnick, B., Williams, D. and Weinstein, M.J. (1963) Pharmacology of gentamycin, a new broad spectrum antibiotic. Antimicrob Agents Chemother. pp. 138.

Bodey, G.P., Middleman, E., Umsawadi, T. and Rodriguez, V. (1972) Infections in cancer patients. Results with gentamycin sulphate therapy. Cancer, 29:1697.

Deveikis, A., Schauf, V., Mizen, M. and Riff, L. (1977) Antimicrobial therapy of experimental group B Streptococcal infection in mice. Antimicrob. Agents Chemother., 11:817.

Edwards, C.Q., Smith, C.R., Baughman, K.L., Rogers, J.F. and Lietman, P.S. (1976) Concentrations of gentamycin and amikacin in human kidneys. Antimicrob. Agents Chemother., 9:925.

Fanning, W.L., Gump, D. and Jick, H. (1976) Gentamycin and cephalothin associated rise in blood urea nitrogen. Antimicrob. Agents Chemother., 10:80.

Gary, N.E., Buzzeo, L., Salaki, J. and Eisinger, R.P. (1976) Gentamycin associated acute renal failure. Arch. Intern. Med., 136:1101.

Goodman, E.L., Van Gelder, J., Holmes, R., Hull, A.R. and Sanford, J.P. (1975) Prospectives comparative study of variable dosage and variable frequency regimens for administration of gentamycin. Antimicrob. Agents Chemother., 8:434.

Gordon, R.C., Regamey, C. and Kirby, W.M.M. (1972) Serum protein binding of the aminoglycoside antibiotics. Antimicrob. Agents Chemother., 2:214.

Gyselynck, A.M., Forrey, A. and Cutler, R. (1971) Pharmokinetics of gentamycin: distribution and plasma and renal clearance. J. Infect. Dis., 124:70.

Hewitt, W.L. (1974) Gentamycin toxicity in perspective. Postgrad. Med. J., 50 (Suppl. 7):55.

Holtzman, J.L. (1976) Gentamycin and neuromuscular blockade (letter). Ann. Intern. Med., 84:55.

Hsu, C.H., Kurtz, T.W., Easterling, R.E. and Weller, J.M. (1974) Potentiation of gentamycin nephrotoxicity by metabolic acidosis. Proc. Soc. Exp. Biol. Med., 146:894.

Just, M., Erdmann, G. and Haberman, E. (1977) The renal handling of polybasic drugs I. Naunyn Schmiedbergs. Arch. Pharmacol., 300:57.

Kaiser, A.B., McGee, Z.A. (1975) Aminoglycoside therapy of gram-negative bacillary meningitis. N. Engl. J. Med., 293:1215.

Luft, F.C., Kleit, S.A. (1974) Renal parenchymal accumulation of aminoglycoside antibiotics in rats. J. Infect. Dis., 130:656.

Moellering, R.C. Jr., Wennersten, C. and Weinberg, A.N. (1971) Studies on antibiotic synergism against enterococci-I Bacteriologic studies. J. Lab. Clin. Med., 77:821.

Records, R.E. (1976) Gentamycin in ophthalmology. Surv. Ophthalmol., 21:49.

Schentag, J.J. and Jusko, W.J. (1977) Renal clearance and tissue accumulation of gentamicin. Clin. Pharmacol. Ther., 22:364.

Warner, W.A. and Sanders, E. (1971) Neuromuscular blockade associated with gentamycin therapy. JAMA., 215:1153.

Weinstein, A.J., Gibbs, R.S. and Gallagher, M. (1976) Placental transfer of clindamycin and gentamycin in term pregnancy. Am. J. Obstet. Gynecol., 124:668.

Weinstein, M.J., Luedemann, G.M., Oden, E.M. and Wagman, G.H. (1963) Gentamycin, a new broad spectrum antibiotic complex. Antimicrob. Agents Chemother., p.1

Wilson, T.W., Mahon, W.A., Inaba, T., Johnson, G.F. and Kadar, D. (1973) Elimination of tritiated gentamycin in normal human subjects and in patients with severely impaired renal function .Clin. Pharmacol. Ther., 14:815.