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Parts II-V of this paper will be published in future issues.

Today's Treatment

Use of antibiotics

Aminoglycosides*

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Indications for clinical use of aminoglycosides in hospital and hospital clinics

LIFE-THREATENING SEPSIS CAUSED BY COLIFORMS, PS AERUGINOSA, AND STAPH AUREUS

Gentamicin and the other systemic aminoglycosides (amikacin and tobramycin) are the first choice antibiotics in life-threatening sepsis caused by coliforms, *Ps aeruginosa*, and *Staph aureus*. Sepsis with coliforms (*E coli*, klebsiella, enterobacter, serratia, proteus, citrobacter), *Ps aeruginosa*, and *Staph aureus* is particularly common in hospital and is more likely to affect debilitated patients such as those undergoing major surgery, those with malignant disease or receiving cytotoxic, steroid, or irradiation treatment, or both, the elderly, neonates, those with indwelling catheters or intravenous lines, and those receiving assisted ventilation. It may present as septicaemia with or without shock, as pyelonephritis, pneumonia, severe wound infection, peritonitis, drip-site infection, hepatic abscess, or cholangitis. In these cases it is imperative to begin antibiotic treatment after specimens such as blood cultures, sputum, urine, wound swabs,

*The first part of Dr Noone's paper was published last week (p 549), together with the tables and references.

etc, have been taken, but before culture and sensitivity test results are available. Gentamicin (or other aminoglycoside) is chosen because of its wide spectrum of activity and its potent, rapid bactericidal action. When the infection is controlled and culture and sensitivity test results are available it may be reasonable to change treatment to some other suitable agent.

In certain cases (generally where mixed bacterial infection is suspected or where synergy is needed) other antimicrobial agents should be combined with gentamicin (or other aminoglycoside).

Anaerobes—Mixed infections including coliforms and anaerobes may be strongly suspected after gastrointestinal surgery or perforation, subphrenic abscess, empyema of the gall bladder, liver abscess, female genital tract sepsis or surgery, aspiration pneumonia, and empyema of the chest. A suitable antianaerobic agent should be combined with the aminoglycoside. The present choice is between metronidazole (my own current preference usually), clindamycin, chloramphenicol, or possibly high dosage erythromycin.

Streptococci—If streptococci are strongly suspected as in endocarditis, cellulitis, or pneumonia, or in patients with hepatocellular liver disease and septicaemia, then a penicillin (benzylpenicillin or ampicillin) should be added.

Staphylococci—When sepsis with *Staph aureus* is strongly suspected as in severe postoperative wound infection, postviral pneumonia, acute endocarditis, then flucloxacillin (or cloxacillin) should be added in high dosage. Although gentamicin (tobramycin) is effective alone against most strains of *Staph aureus*, the high dose of β -lactam antibiotic helps eradicate staphylococci from soft tissues etc.

Neutropenia—The major bacterial pathogens known to infect these patients include coliforms, *Ps aeruginosa*, and *Staph*

aureus. The slow killing of *Ps aeruginosa* by aminoglycosides in the absence of neutrophils prompts the use of carbenicillin with gentamicin (or tobramycin or amikacin) to obtain maximal cidal effect and prevent the emergence of resistance. Carbenicillin alone is inactive against *klebsiella* and some other coliforms and strains of *Ps aeruginosa*.

TREATMENT OF NON-LIFE-THREATENING INFECTIONS CAUSED BY RESISTANT BACTERIA

Treatment of non-life-threatening infections caused by resistant bacteria is chiefly seen in patients with recurrent infections of the urinary or biliary tracts where previous courses of various other agents have been given, and the patient has eventually acquired a multi-resistant hospital strain. The use of gentamicin or other aminoglycoside in such cases should be considered carefully. In a patient with recurrent infection associated with unremediable underlying pathology there is little chance of gentamicin or similar drug being curative (at least not for long) and there is a very real risk of selecting even more resistant bacteria or a fungus in a superinfection. One must ask whether antibiotic treatment is really indicated at all as, for instance, in catheterised patients with "significant bacteriuria" but no symptoms or signs of infection or deteriorating renal function, and, if it is indicated, whether in fact there are other less commonly used, "non-toxic" agents that can be tried instead. Consultation with a clinical microbiologist may be useful for these cases.

Tuberculosis—Streptomycin (and with resistant strains, kanamycin or amikacin) is still widely used in combination—usually with two of the following three drugs, rifampicin, isoniazid, and ethambutol—for an initial three months' treatment. It should be avoided where possible in the elderly and those with poor renal function.

Gonorrhoea—Kanamycin is given as a single intramuscular dose (usually 2 g) on an outpatient basis. It is effective and can be especially recommended when penicillin-resistant strains are encountered. Moreover, kanamycin does not obscure the diagnosis of syphilis. Nevertheless, it is being replaced in this role by spectinomycin, a less ototoxic compound.

Prophylaxis—Gentamicin, tobramycin, and kanamycin have been widely used, usually in combination with penicillins or antianaerobic agents (lincomycin, clindamycin, metronidazole, or erythromycin) in an attempt to reduce postoperative sepsis after gastrointestinal, biliary tract, and other types of surgery. The broad use of aminoglycosides in this way should be discouraged, as it selects for resistance in hospital flora. If prophylactic antibiotics are needed then other agents may be as effective. Bone cement impregnated with gentamicin is widely used on the Continent to prevent sepsis in high-risk orthopaedic surgery such as joint replacement and reparative procedures in already infected bone or joints, and good results have been reported. There is a high local concentration of gentamicin, but serum concentrations are extremely low and toxicity is reputedly not seen. There is at least a theoretical risk of resistant bacteria being selected in the urogenital tract (especially in catheterised patients) by the slow leaking of gentamicin from the cement into the urine in subtherapeutic concentrations over a prolonged period.

Indications for use of aminoglycosides outside hospital

Indications for using aminoglycosides outside hospital are very restricted, and indeed the need to use gentamicin or other aminoglycosides may constitute a valid reason for admission to hospital so that blood concentrations can be monitored and dosage given reliably at regular intervals. Indeed, if the patient is ill enough to warrant gentamicin treatment then this in itself suggests that inpatient care is needed.

Pylonephritis, cholangitis, and sepsis in neutropenic patients are three conditions in which gentamicin may occasionally be indicated in a domiciliary or outpatient setting, but laboratory control of dosage is still indicated.

"Failure" of aminoglycoside treatment

When gentamicin (or other aminoglycoside) is used to treat a susceptible pyogenic infection the response is usually pronounced, even dramatic, and occurs promptly, signs of improvement appearing within a few hours or at most 24-48 hours. A failure of response or further deterioration may suggest one of the following.

A resistant organism—Either naturally resistant such as anaerobes, streptococci, or fungus, or with acquired resistance such as coliform, *Ps aeruginosa*, or *Staph aureus*.

An inadequate dose—Estimation of the peak serum concentrations will help to establish this. The patient may be a "damped responder" or have a "difficult" infection, for instance, *Ps aeruginosa* or coliform pneumonia, when it is important to achieve high peak serum concentrations ($\geq 8 \mu\text{g/ml}$ for gentamicin), presumably to ensure adequate concentrations in respiratory secretions.

An infection in an inaccessible site—Meningitis, thrombosed vein, or an abscess (liver, subphrenic, pelvic, mediastinal, empyema of chest, gall bladder etc)—often indicates a need for surgery. "Good" serum concentrations and a persisting infection often point in this direction.

Neutropenia—Aminoglycosides are much less efficient in patients with few neutrophils, especially with *Ps aeruginosa* infections.

Unfavourable underlying pathology—When this militates against any successful treatment, for instance, patients with terminal liver failure, severe endotoxic shock, carcinomatosis, etc, one cannot expect antibiotics of any kind to work miracles.

Monitoring dosage

Aminoglycosides generally have a low therapeutic index. It is important to give sufficient drug for successful treatment while at the same time avoiding toxicity. Usually successful response is related to peak concentrations, while toxicity is related more closely to trough concentrations (rate of elimination of the drug) than to peak serum values. In table II suitable peak and trough concentrations are quoted for each drug. When trough concentrations are too high it is necessary to reduce dosage, usually by increasing the interval between doses rather than by reducing each dose.

Dosage should be monitored by serum assay, which should be done rapidly (within eight hours). An assay service should be available as an on-call service at evenings and weekends. Ideally, each patient receiving aminoglycosides should be monitored for efficacy (especially in the early stages of treatment) and to avoid toxicity. This may not always be possible but at least the following groups of patients should be monitored: (a) those with impaired renal function or undergoing dialysis; (b) those with septicaemia or (Gram-negative) pneumonia, or both; (c) those apparently not responding to treatment; (d) any patient who has received more than five days' treatment even without obvious impaired renal function; and (e) those who develop symptoms, or signs, or both, of ototoxicity.

The laboratory staff should use whichever assay method they can perform reliably and rapidly. All staff concerned with assay work should be checked at regular intervals by an internal quality control system.

When an assay service is not available, nomograms are a second best substitute. The best nomogram available at present is probably that of Mawer *et al.*⁴ This comes nearest to guaranteeing adequate initial dosage.