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This Week's Citation Classic®

Noone P, Parsons T M C, Pattison J R, Slack R C B, Garfield-Davies D & Hughes K. Experience in monitoring gentamicin therapy during treatment of serious Gram-negative sepsis. *Brit. Med. J.* 1:477-81, 1974.
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We analysed the use of gentamicin in 65 patients with severe Gram-negative sepsis and showed that by ensuring adequate peak blood concentrations of gentamicin in the first 72 hours of therapy, we could achieve cure rates of 84 percent, compared with only 23 percent in those who had inadequate peaks. [The *SCI*® indicates that this paper has been cited in over 205 publications.]

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During the 1960s there was growing recognition of the important role of aerobic Gram-negative rods (Enterobactericeae and *Pseudomonas aeruginosa*) in causing life-threatening hospital-acquired infection, particularly in patients with compromised host defences. Gentamicin, with its reliable and potent bactericidal action against these organisms, was becoming the drug of choice for treating such infections. However, its narrow therapeutic index was a cause for concern, and the idea that blood levels of gentamicin should be measured during treatment to prevent accumulation and toxicity became widely accepted.[1] Various assay methods were developed to improve accuracy and especially speed so that guidance on dosage could be rapid and flexible.

Around that time George Dick moved to the Middlesex Hospital Medical School in London and began building up the Pathology Services and their clinical research activities. I was appointed by him as a lecturer in bacteriology in the company of several enthusiastic young colleagues including John Pattison (now professor of virology in University College London), Richard Slack (now senior lecturer in microbiology in Nottingham University Medical School), and Mike Parsons (now in psychiatry).

With Pattison I had already developed a rapid aminoglycoside assay, and we began to put it into clinical service.[2] Almost at once we realised that the main problem with gentamicin therapy was inadequate initial dosing. Patients with septicaemia were actually dying because clinicians, anxious about toxicity, were failing to give them enough of the drug to achieve any kind of serum concentration adequately exceeding minimum inhibitory concentration values of the infecting organisms.

We quickly found ourselves monitoring gentamicin concentrations to ensure adequate therapeutic dosage rather than to guard against toxicity. This necessitated advising on proper loading doses and checking peak blood concentrations as quickly as possible. It meant providing a 24 hours-a-day, seven days-a-week monitoring service, and it led moreover to even greater clinical involvement in the management of severe hospital infections and in advising on all aspects of antimicrobial therapy.

Each of the main authors analysed the clinical records of a group of patients: Pattison, the urinary tract; Parsons, bacteraemias; Slack, wound infections; and myself, pneumonias.

Our findings accorded well with the clinical experience of many clinicians, microbiologists, and clinical pharmacists and became guidelines for the therapeutic aspects of aminoglycoside monitoring services. The entire monitoring industry took off during the 1970s, and an aminoglycoside assay service became standard in every moderate to major hospital. Our own assay work load at the Royal Free Hospital, where I moved in 1972, increased from 780 assays a year in 1973 (over 90 percent gentamicin) to 4,500 assays in 1986 (aminoglycoside, 75 percent; vancomycin, 25 percent).

Since 1974 many authors have published on the need to monitor patients receiving aminoglycosides, that nomograms are not reliable, and that each patient responds individually but consistently. I have repeated studies on what constituted adequate peak gentamicin levels at the Royal Free Hospital and confirmed our original findings in patients with both bacteraemia[3] and Gram-negative pneumonia.[4]

Some 10 years later R.D. Moore, C.R. Smith, and P.S. Lietman at Johns Hopkins in Baltimore analysed the results of four comparative aminoglycoside studies they had undertaken earlier. They showed a significant inverse correlation between death from sepsis and peak levels of aminoglycosides in the first 48 hours of therapy in patients with Gram-negative bacteraemia;[5] they also showed that peak levels of >7 mg/l for gentamicin and tobramycin and >25 mg/l for amikacin correlated significantly with markedly improved efficacy in patients with Gram-negative pneumonia (78 percent *vs.* 37 percent). Adequate peak serum concentrations were more closely related to outcome of therapy than age, initial peripheral white blood cell count, or renal function.[6]

Perhaps subsequent workers have cited this study because it demonstrates a clear relationship between a "therapeutic" serum level and clinical efficacy, which accords closely with expectations based on *in vitro* work with bacterial cultures. It also shows how the use of a potentially toxic agent with a narrow therapeutic index can be made optimal. This has relevance not only for antimicrobials generally, but also for other classes of drugs, including cytotoxic agents. It forms one of the basic conceptual pillars of any therapeutic drug monitoring service.

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2. **Noone P, Pattison J R & Samson D.** Simple rapid method for assay of aminoglycoside antibiotics. *Lancet* 2:16-9, 1971. (Cited 60 times).
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4. **Noone P & Rogers B T.** Pneumonias caused by coliforms and *Ps. aeruginosa*. *J. Clin. Pathol.* 29:652-6, 1976.
5. **Moore R D, Smith C R & Lietman P S.** The association of aminoglycoside plasma levels with mortality in patients with Gram-negative bacteraemias. *J. Infec. Dis.* 149:443-8, 1984.
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