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#### Concepts for aminoglycoside serum level monitoring

Aminoglycosides are broad spectrum antibiotics of great value in the management of severe Gram-negative infections. These drugs are characterized by a low therapeutic index which can be partly explained by their pharmacokinetic behaviour: namely an uptake into renal tissue with a slow terminal elimination (Kahlmeter, Jonsson & Kamme, 1978; Schentag *et al.*, 1978; Wenk *et al.*, 1979, 1980). The clinical use of aminoglycosides is difficult because of the great variability of serum levels on standardized dosage; a further problem is the dependency of the elimination rate on renal function. Therefore, monitoring of aminoglycoside serum levels is recommended to ensure adequate bactericidal concentrations and to reduce the risks of nephro- and ototoxicity. Despite considerable efforts, however, safe dosage regimens to prevent toxic effects are still lacking.

The attempts to provide the means for improved therapeutic monitoring were more successful, as today at least one dozen different methods are available to measure aminoglycosides in biological fluids. These methods include microbiological plate diffusion assay (bioassay), radioenzymic assay (REA) radio-immunoassay (RIA), enzyme-immunoassay (EIA) and high-performance liquid chromatography (HPLC) (for methodological reviews see Maitra *et al.*, 1979; Reeves, 1980).

How should the routine laboratory select the most suitable method? This question cannot be generally answered as every laboratory is faced with different working conditions. However, careful consideration of the established criteria, such as specificity, sensitivity, accuracy, time requirement, ex-

penses for trained personnel and reagents, is very useful. In addition, the aminoglycoside measurements should be coordinated with the overall drug monitoring programme of a hospital, which not only includes the aminoglycoside antibiotics, but also the whole spectrum of drugs, fulfilling the basic requirements for serum level determinations (Richens & Warrington, 1979).

What does this mean for the choice of an assay to measure aminoglycoside antibiotics? First, to reduce costs for equipment and personnel, there is no longer a justification to develop a separate assay technique for every single drug included in a monitoring programme. It is more reasonable to use a limited number of assay systems which can deal with most of the drugs selected for serum level determinations. Some of the more popular aminoglycoside analyses have to be discussed in the light of this concept. The bioassay is probably still the most widespread method, but the reasons for this are historical rather than objective advantage. The bioassay is non-specific and time consuming, and its accuracy can be very poor if the method is not performed under skillful supervision. The latter implies additional efforts in personnel and cost, an aspect which is very often disregarded by authors discussing this method.

The radioenzymic assay is a highly reliable tool to measure aminoglycosides, but it also needs close attention and an expensive liquid scintillation counter. Furthermore, this method cannot be used for any other drug.

High-performance liquid chromatography as well as immunological methods belong to the techniques applicable to a wide variety of organic substances: they are sensitive, accurate and highly specific. Unfortunately, the aminoglycosides can be assayed by HPLC only after pre- or postcolumn derivatisation, because they have a poor UV-absorption in their un-derivated state (Anhalt & Brown, 1978). In addition, HPLC is relatively inflexible for routine use, especially if different drugs have to be analysed regularly. This drawback might be overcome either by the rather expensive way of using a separate HPLC equipment for each drug or by adding a column switching device to have different equilibrated columns at hand. This technique can also be used for an on-line sample clean-up, a very promising new way for the sample preparation (Erni *et al.*, 1981).

Radioimmunoassays are commercially available for most aminoglycosides and also for a great number of other drugs. If a

laboratory is working predominantly with RIAs it has to deal with assays from several different manufacturers. This can be a serious source of errors. Furthermore, the limited shelf-life and the hazards of working with radioactive materials are other disadvantages of the radioimmunoassay. However, because of its extreme sensitivity, RIA will still be the method of choice for certain pharmacokinetic studies.

At present, there is a trend leading away from radioimmunoassay to non-radioactive enzyme-immunoassays or fluoroimmunoassays. In fact, the commercially available homogenous enzyme-immunoassay (EMIT, Syva Corp., Palo Alto, CA) would well fit into the more generalized monitoring concept mentioned above. With this technique it is not only possible to measure the aminoglycosides (gentamicin and tobramycin are already available, reagents for netilmicin and amikacin are in preparation), but also several other drugs requiring therapeutic monitoring, e.g. antiepileptics, antiarrhythmics, theophylline and methotrexate. The relative high costs for the EMIT kits are partially compensated by the great saving in time, and furthermore, economies are possible by automated procedures. Another promising non-radioactive immunological technique is the fluoroimmunoassay, but so far the reagents for only a limited number of drugs are available.

Whichever assay is used, one should always keep in mind that only accurate blood level determinations are of value for the clinician and, above all, for the patient. The introduction of commercially available tests, which are easy to perform, and consequently also permit smaller laboratories to carry out drug level determinations, may lead to a rather uncritical handling of the results. An extensive quality control program, which should include external control samples, is therefore another essential aspect of drug analysis. The importance of quality controls was demonstrated by Reeves (1974). In a survey of the accuracy of gentamicin analysis among more than 80 laboratories only about 20% of the participants produced satisfactory results. At that time, however, mostly bioassays were used. The current results of the quality control program organized by the American Association of Clinical Chemistry looks much more optimistic, especially for those laboratories performing their determinations by RIA or EMIT.

The potential benefit of rational therapeutic drug monitoring is now widely

accepted. Education in clinical pharmacology as a new clinical speciality is also established in most medical universities (Spector, Roberts & Vessell, 1981). This is an important requirement, as drug level measurements without expert advice by a clinical pharmacologist or by a clinician trained in this field are often of questionable value. The availability of sophisticated analytical techniques should not distract our attention from the clinical situation and the aim of aminoglycoside monitoring. There is always a danger of treating the serum levels rather than the patients.

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