An Emotional-Based Medicine Approach to Monitoring Once-Daily Aminoglycosides

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As the concepts of evidence-based health care become entwined into pharmacy practice, it is interesting to watch the use and monitoring of once-daily aminoglycosides (ODA) evolve. Many years ago, the monitoring of aminoglycoside serum concentrations was an inroad that allowed us, as hospital pharmacists, to get up on the wards and become directly involved in patient care. Fortunately, this practice was developed before the advent of evidence-based health care because the evidence to support aminoglycoside serum concentration monitoring was suspect at best.

Monitoring of Serum Concentrations for ODA

Over the last few years, dosing of aminoglycosides has changed and many hospitals have adopted the concept of ODA dosing. It appears that the majority of those who now use ODA dosing also measure aminoglycoside serum concentrations in patients receiving this regimen. Authors of a survey from 1995 reported that of the 19% of hospitals that used once-daily dosing, most measured concentrations. Seventy percent measured peak and trough concentrations, 5% measured peaks, 10% troughs, 3% 18-hour concentrations, and 12% other concentrations. In a more recent Canadian survey, 77% of respondents stated that ODA was used at their hospitals. Eighty-six percent reported that serum concentration monitoring was done. Peaks and troughs were measured 28% of the time, only troughs 61% of the time, only peaks 7% of the time, and a single concentration 4-18 hours after the dose 34% of the time. Most recently, a national survey of acute care hospitals in the United States found that 60% of surveyed hospitals measured a single concentration at 6–18 hours and 31% measured only troughs.

Evidence for Peak Serum Concentrations and Outcomes

There is a large body of literature that has looked at the relation between aminoglycoside serum concentrations and outcomes and toxicity for multiday dosing. Almost none of it, however, stands up to critical appraisal. In addition, peak levels achieved with ODA dosing are 2–3 times those seen with conventional or multiday dosing. For these reasons, it is likely not valid to extrapolate these data when one is trying to establish serum concentration monitoring guidelines for ODA.

Evidence usually is categorized into five levels. These levels are, in descending order of importance, randomized controlled trials, cohort studies, case-control studies, case series, and expert opinion without explicit critical appraisal or based on physiology, bench research, or “first principles.”

A thorough literature search produced no supportive evidence for ODA serum concentration monitoring that fit into any of the first four levels of evidence. Clinicians who routinely monitor ODA concentrations may find this somewhat surprising. In contrast, there are examples of case-control studies that appear not to support a relationship between peak serum concentrations and outcome. Researchers found that peak serum concentrations in patients receiving ODA did not correlate with outcomes.
Evidence for Trough Serum Concentrations and Toxicity

In one study initial trough serum concentrations were higher (1.2 vs 0.5 mg/L) in patients who developed toxicity, but a later study found that trough levels were not a risk factor for toxicity. One researcher found that mean maximal trough serum concentrations were higher (4.4 vs 0.9 mg/L) in patients who developed nephrotoxicity, but “no causal relation could be found in time between the rise of the serum creatinine and serum trough levels,” which should question the utility of measuring aminoglycoside concentrations to decrease the chance of nephrotoxicity. Another study determined that mean maximum trough serum concentrations were higher (2.8 vs 1.1 mg/L) in patients who developed nephrotoxicity but did not report whether there was a causal relation. It is unknown, but increasing trough serum concentrations may be due solely to reductions in drug clearance secondary to nephrotoxicity rather than the cause of nephrotoxicity.

Evidence that Monitoring Serum Concentrations in Patients Receiving ODA Improves Outcomes or Reduces Toxicity

No randomized controlled trials, cohort studies, or case-control studies were found.

What is the Evidence for Monitoring Serum Concentrations in Patients Receiving ODA?

The fifth or lowest level of evidence includes expert opinion without explicit critical appraisal or based on physiology, bench research, or first principles. This seems to be where almost all the evidence for monitoring concentrations for ODA resides. Opinions come from a variety of sources.

Opinions on Peak Serum Concentrations and Outcomes

The authors of a commonly quoted article from 1995 state that the reason for using a peak concentration of 20 mg/L is that “one generally targets the most troublesome pathogen...at our institution this organism is P. aeruginosa (median MIC [minimum inhibitory concentration] 2 mg/L)...as a result we designed a drug administration that would produce concentrations at 1 hour of approximately 10 times the gentamicin MIC or 20 mg/L.”10 One easily can see some of the potential flaws of this recommendation. What is the clinical evidence that a peak concentration 10 times the MIC is needed to improve outcome? Why was the median MIC chosen? Doesn’t using the median MIC mean that half of all patients would not have adequate aminoglycoside serum concentrations? What if an organism other than P. aeruginosa causes the infection? What if the infection is in an area where aminoglycosides either penetrate very easily or very poorly? What if other antibiotics are being used at the same time?

Authors of a 1999 review article on ODA state that a peak concentration of 10 mg/L was the concentration that was “critical...for efficacy” yet provide no rationale or references that support this comment.11 Other authors provide a protocol with a variety of peaks, troughs, and 18-hour concentrations but, as with other articles, provide no references that support the numbers in the table.

Other recent writings on ODA contain interesting quotes such as, “our findings of variable PK [pharmacokinetics]...in critically ill surgical patients suggest frequent aminoglycoside monitoring is needed...to assure achievement of therapeutic drug concentrations” but provide no references to support this statement. Even authors who disagree with ODA give the following as a reason for concern: “single daily dosing...does not provide optimal peak concentrations in many patients...this is exceedingly important.”14 None of these quotes refers to clinical trials that have to do with ODA and appear to be simply opinions.

Opinions on Trough Serum Concentrations and Toxicity

One article stated that the researchers used a “drug free period (concentration < 0.5 mg/L) of at least 4 hours,” but again no references support the practice. In general, most recommendations suggested that the trough concentration should fall below 2 mg/L, but I could not find any evidence to support this recommendation.

Summary of Evidence

In my review of the literature, no clinical trials show or suggest that monitoring of serum aminoglycoside concentrations for ODA is of benefit. In addition, there are almost no studies that have evaluated whether certain concentrations achieved with ODA are associated with therapeutic outcomes or toxicity. All we have is expert opinion. Given this, I would like to add my opinion.
What Should Be Monitored?

Given the lack of clinical trial evidence, I find it difficult to justify any monitoring of serum concentrations in patients receiving ODA. So what should one monitor?

Efficacy obviously can be monitored by assessing how the patient feels, noting the clinical response of the patient using parameters such as temperature, white blood cell count, and depending on the infection, the degree of inflammation, and looking for reversal of whatever evidence there was for an infection in the first place.

With regard to toxicities, the most serious and life-altering adverse effects from aminoglycosides are auditory and vestibular. These primarily occur in patients who have been receiving these drugs longer than necessary. I have been involved in four aminoglycoside (three in Canada, one in the United States) ototoxicity lawsuits (fortunately not against me) where I was an expert witness, and without exception the problem was that the aminoglycoside was continued for far longer than was necessary. Embarrassingly, pharmacists often were involved; they had monitored serum concentrations but had not effectively clinically monitored the patient. I have spoken to hundreds of pharmacists who follow patients receiving aminoglycosides, and I can count on the fingers of one hand those who stated they ever clinically monitored the patient. I have spoken to hundreds of pharmacists who follow patients receiving aminoglycosides, and I can count on the fingers of one hand those who stated they ever clinically monitored the patient.

As a further example of the irony, a 1999 review entitled "Some international approaches to aminoglycoside monitoring in the extended dosing interval era" reports on the monitoring that occurs at a group of centers from around the world. In the nine pages of text, there are numerous comments on monitoring serum concentrations and renal function, but monitoring for ototoxicity is not mentioned anywhere.15

In my opinion, patients who are receiving aminoglycosides for more than a couple of days should be told about the potential of aminoglycosides causing ototoxicity. In addition, clinicians should ask patients about the following signs and symptoms on a daily basis: tinnitus, loss of hearing, a sense of fullness in the ears, headache, nausea and vomiting, giddiness, lightheadedness, vertigo, nystagmus, and ataxia. If any of these occur, and there is no other reasonable cause, the aminoglycoside should be discontinued.

Is monitoring of ototoxicity possible in every patient? Of course not—in the intensive care unit, almost none of these signs and symptoms can be evaluated. So, in these patients, every attempt should be made to minimize the duration of aminoglycoside therapy. With available alternatives, there are very few clinical circumstances (other than for some cases of osteomyelitis or endocarditis) where aminoglycosides need be given for greater than 7–10 days. Often there is little reason to continue aminoglycosides beyond 3–4 days.

Although nephrotoxicity is a concern, it is usually reversible. Monitoring of serum creatinine every 2–3 days should be sufficient to identify those patients whose serum creatinine concentrations are increasing. If serum creatinine increases by more than 25–50%, the aminoglycoside should be stopped and replaced with an agent that is less nephrotoxic such as a penicillin, cephalosporine, or quinolone. If the aminoglycoside absolutely must be continued or used in patients with an estimated creatinine clearance of less than 60 ml/minute, empiric dosage adjustments (increasing the interval to the next useful dosage interval) should be made.16

Am I right or wrong in my approach to monitoring? Am I right or wrong not measuring serum concentrations? I don't know, but no one knows because we don't have any nonopinion evidence that helps us answer these questions. However, my approach does avoid the cost and inconvenience of measuring aminoglycoside concentrations, forces me to clinically monitor patients to the best of my ability, and encourages the briefest possible course of aminoglycoside therapy. In addition, it allows the patient to be informed of the risks and be involved in the decision-making.

Many clinicians consider aminoglycoside serum concentration monitoring to be a standard of care, and the product monograph states that "serum concentration monitoring of aminoglycosides should be done when feasible." The law imposes on a practitioner a duty to exercise reasonable care and skill in the provision of professional advice and treatment. Any clinician who clinically evaluates the patient daily for efficacy (resolution of signs and symptoms of an infection) and toxicity (measuring serum creatinine 2–3 times a week, asking the patient daily about signs and symptoms of ototoxicity),
and involves the patient in the decision-making is exercising reasonable care whether or not serum levels are monitored. In fact, from my experience, they are doing more than what is done by the vast majority of clinicians who monitor patients receiving aminoglycosides.

Unfortunately, I have to end this commentary with the old cliché: more studies are required to determine the role of monitoring ODA concentrations because we have virtually nothing but opinion.

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References