A Case for the Lowly Case Report

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The standard for the most valuable and highest level of scientific evidence is a systematic review using a meta-analysis. By combining the results of all available randomized clinical trials, a meta-analysis can confirm the relative efficacy of a treatment. The importance of the case report is that it identifies and documents unusual and unexpected events. By identifying potential and rare risks, a case report is often the first step in determining the safety of a treatment. A carefully documented case report allows readers to reflect on their own treatment experiences. Several examples of the importance of the lowly case report are presented.

Biomedical research is the foundation of anesthesia and therapeutics. And it constantly brings us new and often confusing concepts. When I first heard the term “molecular biology” I was confused; “Aren’t all cells made of molecules?” Then came “evidence-based medicine,” quickly followed by “evidence-based dentistry” (we didn’t want to miss this train). Again I was confused; “What do these people think I’ve been doing for the last twenty years: picking treatments at random?”

I have come to appreciate the clinical importance of evidence-based practice. I’ve learned the specific methods used with systematic reviews and the appropriate application of their conclusions. My students are now taught the hierarchy of scientific evidence needed for clinical decision-making. This hierarchy ranges from opinion, to case reports, to case-series, to surveys, to cross-sectional epidemiology studies, and to multicenter randomized controlled clinical trials.¹

The most reliable evidence available to base clinical decisions is the systematic review using a meta-analysis. By combining the results of all reliable published and unpublished randomized clinical trials, a meta-analysis can confirm the relative efficacy and consis-

tency of a treatment. Unfortunately, with the introduction of meta-analyses, we were required to learn how to interpret those pesky statistics: NNT (number needed to treat), NNH (number needed to harm), and CI (confidence intervals).²

The conclusions of these summary analyses provide the evidence for “what works best.” A good example of a meta-analysis was a publication in this journal by Ahmad et al that evaluated the evidence for the relative efficacy of analgesics used in dentistry.³ By reviewing the available evidence from 33 published randomized controlled clinical trials, the authors concluded that, collectively, the literature consistently finds many nonsteroidal anti-inflammatory drugs (NSAIDs) more effective than acetaminophen 650 mg with codeine 60 mg.

One can hardly argue that randomized controlled clinical trials are not a powerful research method for determining the efficacy of an intervention or new drug, and that this information is essential in selecting a treatment most appropriate for a patient’s care. But ultimately the decision for what is the most effective treatment must be balanced by the potential risk. One treatment may be the best, but may not be the safest.

Clinical trials do assess safety and report common adverse drug reactions such as nausea, vomiting, respiratory depression, or headache. But if the adverse event is rare, or occurs only after prolonged treatment, or is seen only when a patient has a specific disease, or occurs only when taking another drug, clinical trials are unlikely to recognize the adverse outcome.

Here lies the importance of the lowly “case report.” A well written, carefully documented case report is often the first indication of an unexpected and rare adverse event. When published in a journal, it allows other practitioners to reflect on their own treatment experiences. If submitted to the FDA’s MedWatch registry of adverse events, a case describing an unexpected adverse event can be added to a database of unusual relationships.⁴ When reviewed by the FDA, two similar unusual events will provoke suspicion. Any additional reports can invoke serious repercus-

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sions (even the FDA uses the “three strikes and you’re out” rule).

Given the risk averse nature of dentists, the possible occurrence of an extremely rare adverse event can significantly affect decision-making. In dental anesthesiology, rare events are often life-threatening. Knowledge of potential risks can significantly impact our training, our monitoring requirements, our treatment and prevention guidelines, and our standard of care. Case reports are the initial step in establishing the existence of rare adverse events.

For example, anesthesiologists use protocols to prevent and treat malignant hyperthermia, an unknown phenomena prior to 1960. The case report by Denborough et al published in 1962 alerted anesthesiologists to the familial relationship of this rare and misunderstood life-ending event.⁵ Only after publication of this case report was the puzzle of malignant hyperthermia and its etiology revealed.

Approved by the FDA in 1985, terfenadine (Seldane) was the first prescription antihistamine that didn’t cause drowsiness. A single report of a drug reaction in a 39-year-old woman ultimately contributed to the removal of the terfenadine from the market in 1998. Torsades de pointes, a drug-induced ventricular tachycardia associated with prolongation of the QT interval, had been described. This report first described the association of symptomatic torsades de pointes occurring with the use of terfenadine in a patient who was taking the recommended prescribed dose of this drug in addition to ketoconazole.⁶

A similar history exists for the NSAID zomepirac (Zomax). In 1981, Samuel reported a case of anaphylactic shock associated with its use.⁷ Several additional reports followed as practitioners began to recognize the anaphylactoid potential of zomepirac. Eventually, the drug was removed from the market.

Consider the drug interaction between levonordefrin (Neocobefrin) and propranolol (Inderal) reported by Mito and Yagiela.⁸ Prior to this report, the potential for a nonselective beta-adrenergic antagonist to induce a hypertensive response following the injection of a dental local anesthetic containing epinephrine or levonordefrin had been considered clinically insignificant. Since publication of this well-documented case report, this clinically relevant drug interaction has become common knowledge for most dental practitioners.

Yes, case reports have weaknesses. They may not prove causation and may in fact be documentation of pure coincidence. The description of events may not be reliable or valid. They provide qualitative information, not quantitative. Even a case-series of several similar adverse events, such as local anesthetic toxicity reactions in children, cannot provide information regarding the rate at which the

local anesthetic toxicities occur.⁹ Case reports do not provide adequate information to determine whether the adverse event occurred once in a 100 treatments or once in a 1,000,000 treatments.

I am generally attracted to the case report section of a journal and am not surprised when morbidity conferences describing unusual cases are well attended. Describing a real event brings the learning to a personal level. It begins with the “this is clinically important for you” rather than ending a long lecture of didactic information with “this may possibly be important some day.”

Case reports teach in a practical way, involving inductive reasoning rather than deductive reasoning. When something unexpected occurs during treatment of a patient, we must search our memory for principles and concepts that explain what is happening. This deductive process, from a single event to a generalized concept, is the pathway followed within a case report. Probably my most read publication was a concise case report of a local anesthetic overdose of a pediatric patient. The discussion was most appreciated because it reiterated the importance of dose calculations, prevention, and emergency management.¹⁰

So I applaud *Anesthesia Progress* for their support of the lowly case report. I encourage our members, practitioners, and students to submit, and I thank the authors of recent case reports, Drs. Webb and Unkel, Dr. Mohri-Ikuzawa, and Dr. Prior, for keeping me informed, allowing me to reflect on my experiences, reeducating me of knowledge forgotten, and reminding me to always be vigilant.^{11–13}

Case reports provide an essential piece of evidence needed for evidence-based practice. And best of all, there are NO STATISTICS.

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