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EDITORIAL

What To Do with Case Reports: Is Folly That Succeeds Folly Nonetheless?

Clinical toxicology is a rapidly evolving discipline. Each new pharmaceutical agent, illicit drug, industrial chemical, and household product carries the potential for human toxicity. In addition, combinations of these agents offer limitless possibilities for adverse events, all of which need to be interpreted and shared. Case reports provide the perfect forum for the initial discussion of these observations. Yet, applying the data gained from case reports to daily practice is often difficult. The evidence-based approach assigns very little power to case reports because of their limited ability to confirm associations, rare ability to assign causation, and complete inability to calculate incidence or prevalence. As such, changing practice based on case reports is inherently dangerous.

For example, shortly after the introduction of tricyclic antidepressants (TCAs), their cardiovascular and neurological toxicities were rapidly appreciated. Case reports in the early to mid-1970s suggested that administration of physostigmine was beneficial (1–4). Animal models were contradictory, showing minimal benefit (5) or clear exacerbation of toxicity (6). Despite this, noted toxicologists of the time recommended physostigmine and countless patients were treated. Although it is unclear how many benefited from this practice, it is probably safe to say that it was without harm for the majority. Despite the fact that no controlled study of physostigmine in humans with TCA was ever published, the practice of routine administration of physostigmine to patients with TCA toxicity continued. Several years later, two cases of asystole temporally related to physostigmine administration raised concern about this practice (7). After subsequent reevaluation of the data, risks, benefits, and alternatives therapies (such as sodium bicarbonate) physostigmine was abandoned as an antidote for patients with TCA toxicity, but this process took years. By today's standards, the initial case reports would have been deemed insufficient by many clinicians to begin the routine administration of physostigmine without sound animal data or a human trial.

Conversely, had there been reasonable data to support the use of physostigmine in this setting, the cases presented by Pentel and Peterson would have been judged inadequate to alter practice, as a causal relationship between physostigmine use and asystole was challenged by several prominent clinicians of the time.

In the current issue of *J. Toxicol.—Clin. Toxicol.* Van Deusen et al. present an interesting case report of an 89-year-old woman with a wide-complex bradycardia and altered mental status (8). In addition to being treated with a transvenous pacemaker, she was given dextrose, insulin, calcium chloride, and furosemide when her potassium was found to be 9.9 mmol/L. Subsequently, her serum digoxin level was reported as 8.4 ng/mL. Digoxin-specific Fab were administered, she underwent hemodialysis for hyperkalemia, and ultimately did well. The authors review the limited human case reports and the somewhat conflicting animal data that gave rise to the dogma that calcium salts are contraindicated in cardioactive steroid toxicity. They also question the frequently offered suggestion that transvenous pacemakers are contraindicated in the setting of cardioactive steroid toxicity, a caveat drawn from a a single study (9). Although they correctly call for a more thorough evaluation of the problem, it is unlikely that any ethics committee would approve a randomized human trial.

So, how are we to interpret their presentation and analysis of the literature? Life has taught us that there

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are very few "all-or-none" types of events. The concept of dose-response, which is a fundamental tenet of clinical toxicology, mandates that phenomena usually only occur a percentage of the time, even when pre-existing criteria are well met. In other words, there are no guarantees. For example, most readers will believe that there are valid data to support an adverse drug interaction between monoamine oxidase inhibitors (MAOIs) and meperidine. Yet at some dose, in an animal model this reaction would only occur in a minority of animals treated. Based on these data, would it then be acceptable to prescribe meperidine to a patient receiving phenelzine? The answer, of course, is no. It is the process of arriving at this answer that provides us with a framework for the interpretation of case reports.

When case reports suggest causation, Hill's criteria should be applied (see Table 1(10)). However, even if we believe the criteria for causation have been met, case reports can never tell us about incidence or the reproducibility of the observed finding. Ultimately, when a new therapy is suggested, we perform an informal assessment of the risk-to-benefit ratio of the new treatment in comparison to alternatives to help ascertain the merits of the case report. The risk is calculated from the understanding that the reaction may occur and supported if the probability of that reaction is actually known. The benefit relates to the value of the intervention and is always interpreted in light of the competing risks of alternative therapeutic options.

Thus, in the previous example the analysis favors not administering meperidine to a patient treated with phenelzine because of the potential risk and, more importantly, the availability of safe and effective alternatives such as morphine. Certainly it is possible that meperidine could be administered to a patient receiving an MAOI without adverse reaction. This, however, does not make that practice advisable. Thus, the dogma is not based exclusively on the probability of an event occurring, but on the risk-to-benefit analysis of the entire scenario.

In the current discussion, Van Deusen and colleagues are absolutely correct to question the foundation for the dogmatic statements that link calcium and transvenous pacemakers to cardioactive steroid toxicity. Yet there are other real questions that need to be asked:

1. In the setting of cardioactive steroid toxicity, hyperkalemia represents a shift from the intracellular to the extracellular space coupled with an intracellular increase in calcium. Total body potassium is normal, or even somewhat low if renal compensation has begun. This is, therefore, distinctly different from the total body potassium overload and calcium deficiency that occur in patients with renal failure. The question to be asked is whether there is any evidence to suggest that exogenous calcium would provide the same beneficial alterations on membrane potential in the setting of cardioactive steroid toxicity as it does in the hyperkalemia of renal

Table 1. Hill's criteria for causation.

Criteria	Explanation
Strength	The link between events should bewell founded. One way to express this is with a high relative risk.
Consistency	The relationship is supported by multiple studies in different populations, models, or species.
Specificity	The observed result does not occur (or occurs vary rarely) without the presumed cause.
Temporality	The cause should precede the effect. The more reproducible the time between the cause and effect, the stronger the argument.
Biological gradient	There should be a good dose-response curve.
Plausibility	Current scientific understanding should support the association.
Coherence	The association should not conflict with generally known facts.
Experiment	The association should be demonstrable with a well-designed study.
Analogy	Does the association closely resemble another causal relationship that has already been accepted.

Adapted from Hill, AB: The environment and disease: association or causation? *Proc R Soc Med* 1965; 58: 295.

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failure? And what other methods are available to treat cardioactive steroid-induced hyperkalemia?

2. Additionally, is there any evidence to suggest that transvenous pacemakers improve outcomes in patients with cardioactive steroid-induced bradycardia? What other methods are available to treat this bradycardia?

I would argue that because there is no proven benefit for calcium in the setting of cardioactive steroid toxicity, and since insulin, dextrose, bicarbonate, sodium polystyrene sulfonate, and digoxin-specific Fab all lower serum potassium safely, prudence dictates that if there is **any** possibility of serious harm with calcium administration, it should be avoided. Similarly, since data presented by Taboulet et al. suggest that transvenous pacemakers are associated with worse outcomes than digoxin-specific Fab, even though transvenous pacemakers may be safe and effective in some patients, digoxin-specific Fab would always be preferred because of its safety (9).

The "dogma" is not "calcium administration or a transvenous pacemaker plus digoxin equals death," but rather "based on the available information it is inadvisable to administer calcium or insert transvenous pacemakers in patients with cardioactive steroid toxicity." The use of calcium and a transvenous pacemaker in the present case without harm provides insufficient evidence to overthrow the existing doctrine. Importantly, the report by Van Deusen and colleagues reminds us that we should challenge dogma when it exists and forever seek the best therapy for our patients. In addition, we should not be quick to scorn the use of pacemakers and calcium when the diagnosis of cardioactive steroid toxicity is unknown.

The utility of case reports is in their ability to rapidly present new material, challenge dogma, and make us think and rethink our thought processes and practices. The associations they describe serve as wonderful starting blocks for formal studies. However, association does not equal causation, and rarely should a single case report or a small case series provide sufficient grounds to overturn existing standards that are founded upon experience and reason, even if not by irrefutable science.

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