Insidious cardiotoxicity:
Ubiquitous and important, but difficult and expensive to predict! Work in progress!

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If we knew it was going to come on, maybe we could have sought a different molecule or intervened!! But who conducts studies to predict such an insidious outcome?

The “whole story”!

6 weeks old 9 months old = 18 years!

doxorubicin
Introduction

Cardiovascular functions (e.g., chronotropy, dromotropy, bathmotropy, inotropy, lusitropy, ventriculo-vascular coupling, vascular capacitance, baroreceptor control) may be affected by drugs or devices in a manner that leads to morbidity and/or mortality, peracutely [within seconds of exposure (e.g., strychnine, tetrodotoxin, dofetilide)], or insidiously requiring weeks to decades during or after exposure (e.g., lead, arsenic, doxorubicin, trastuzumab, sunitinib, digitalis, fenfluramine-phentermine). Agreement on the name (i.e., peracute, acute, chronic, subchronic, insidious) of a duration between dosing and when toxicity is observed may be absent, but everyone recognizes strychnine and tetrodotoxin toxicities as per-acute, and at least 1 manifestation of doxorubicin and/or fenfluramine-phentermine toxicities as insidious. And of course, everyone knows that duration between dosing and toxicity is influenced by dose, potency, and by kinetics of absorption, distribution, and binding.
Usually chronic toxicity is considered a non- or sub-lethal set of signs and/or symptoms (e.g., heart, renal, or hepatic failure, decreased growth, infertility, behavioral changes) resulting from lengthy exposures to a chemical and/or mechanical or psychological stress. Here we define insidious toxicity, however, as occurring during or after exceptionally lengthy, and putatively therapeutic exposures. Does that sound familiar? Identifying peracute risk is usually relatively simple, precise, and inexpensive; identifying toxicity to chronic risk is less so; identifying insidious risk is much more complicated, slow, faulty, and costly. Do you think that this means we must conduct preclinical trials for 18 years before initiating a phase I clinical trial? Listen on!
Compare, for example, cost time, and effort for preclinical and clinical trials designed to predict the potential of acute toxicity to strychnine, to trials designed to predict potential insidious toxicities to decades after receiving doxorubicin, years after drinking water laden with lead, or months after taking fenfluramine-phentermine for obesity! What is the balance between paying for a preclinical trial that may predict insidious toxicity versus the cost in dollars, time, lives, and reputation of an adverse event discovered after marketing? Any way you “cut it”, whenever we ask to do what may take time, cost money, delay marketing, or diminish specificity, get ready to defend it.
Many instances of drug-induced myocardial toxicities stem from rather acute, direct, specific, destructive, cytotoxic actions of drugs (e.g., apoptosis, lysis, coagulation), however it is well-known that drug-induced toxicities may result from insidious, long-term, energetic imbalance due to a mismatch between ATP production and demand. Another relevant finding is that a drug may allow one to feel better in the short-run, but die sooner (e.g., treating heart failure with dobutamine, furosemide, milrinone, or digitalis), versus making one feel worse in the short-run but feel better in the long-run and live longer (e.g., carvedilol, captopril, spironolactone).
Whether energetic imbalance translates to morbidity and/or mortality, and for how long and to what degree the imbalance must exist before toxicity develops, may be expressed in a paradigm (chronaxie and rheobase) used by neurophysiologists to express the magnitude and duration of a stimulus required to produce a response.
Anybody can predict [rapidly and cheaply (in yellow)] likelihood of toxicity to strychnine; but it is difficult, costly, and time-consuming to predict likelihood for doxorubicin (green)! “Borrowed” from how the neurophysiologist describes excitability; how we may describe relation of exposure (amount and duration) and liability. **Chronaxie for cardiomyopathy may be 18 years!**

**Diagram:**
- **Strychnine** and **doxorubicin** are depicted on a graph with **strength** on the y-axis and **time** on the x-axis.
- The graph shows the concept of **chronaxie**—the time required for a current (dose of Rx) twice the rheobase (threshold) to illicit a response.
- The curve for doxorubicin is shown to be much flatter than for strychnine, indicating a longer time for a response.
This session discusses: (A) properties of cardiovascular function for which insidious toxicities have proven important, (B) methods (e.g., parameters, instruments, models) for how those functions may be interrogated to predict insidious toxicity, (C) changes in function that may predict morbidity and/or mortality, (D) relative costs to predict insidious toxicity? You realize that what could follow constitutes an entire, life-time curriculum in cardiovascular physiology / pharmacology / pathophysiology / toxicology, so because of time constraints, I’d like to present some general information on insidious toxicity, use a prototypical molecule—doxorubicin—that possess multi-cellular, multi-tissue effects some that are acute, some chronic, and some insidious, and allow the participants to question, challenge, supplement, and otherwise discuss the topic.
IIA

Properties of cardiovascular function that may be investigated because they might predict outcome to patients or of drugs: [Renamed: Which properties do you not want to explore? And again, what does it cost when an adverse event occurs?]

Theme: You don’t have to explore anything. The more you explore the more you have to explain, the greater the chance of a superfluous finding, and the greater the chance of an important finding.

1. Electrophysiological: chronotrope, dromotrope, bathmotrope
2. Mechanical: inotrope, lusitrope
3. Integrative: stroke volume (SV), cardiac output (CO), distribution of CO, aortic pressures (AoPs), venous pressures (Pv), vascular resistances (svr, pvr)/impedances (Z), capacitances, reactivities, ventriculo-vascular coupling, high- and low-pressure baroreceptor sensitivities, energetic balance
What G. Zbinden and I think!

Don’t select a species or do something: (a) because you can, (b) because others do it, (c) because it’s always been done, (d) because you think it may be expected, (e) unless you know how to interpret results. Do something because there is evidence it will provide an answer important to achieve agreed-upon goals; it should make a difference! Differences must have been shown to assist in achieving goals and not to produce risk of expensive/time-consuming surveillance.

Everyone knows polymorphisms are where it’s at!

Which do regulators want?
Which represents your patients?
Which do statisticians want?
Some issues to be addressed about a model-study before selection of a model!

- Seeking knowledge for: statistical validity, publication, submission to regulatory agency, “in-house” decisions?
- What are properties (e.g., solubility, protein-binding, pharmacokinetics, in particular organs of metabolism/excretion) of chemical(s) to be studied?
- For what demographic (e.g., males, females, size, diabetics, obese, neonates, senile) and target species is knowledge to be applied?
- What is the pathophysiology of indication (e.g., diastolic heart failure, systolic heart failure, arrhythmia, pulmonary hypertension, renoprival systemic arterial hypertension)?
- What are putative mechanisms of action (e.g., inotrope, lusitrope, ventricular-vascular coupling, non-cardiac) of test article?
- GLP versus in spirit of GLP?
IIB Devices and methods:

- Signalment & History
- Physical exam (murmur)
- Radiographic findings
- ECG
- Echocardiography
- Clinical Pathology
Left Ventricular Pressure (Baseline)  (6 weeks after embolization and doxorubicin)
Measures used to identify contractility:

1. \(dLVP/dt_{\text{max}}\)
2. Time to \(dLVP/dt_{\text{max}}\)
3. \(dLVP/dt_{@LVP=30}\)

M-mode echocardiogram showing how left ventricular preload could be measured non-invasively and precisely.
TEST:  What does drug do?

Encircle properties of drug?
+ inotrope
- inotrope
0 inotrope
+ chronotrope
- chronotrope
0 chronotrope
+ lusitrope
- lusitrope
0 lusitrope
arteriolar vasoconstrictor
arteriolar vasodilator
no arteriolar vascular effect
arterial vasoconstrictor
arterial vasodilator
no arterial vascular effect
energetic imbalance
energetic balance
no change in energetics
A modified Wiggles diagram showing cardiovascular pressures, volumes, wall thickness, and myocardial tension. Left ventricular tension (left ventricular pressure times left ventricular volume (actually radius), all divided by left ventricular wall thickness) is shown in solid red. Peak tension—the measure of afterload (AL)—occurs at vertical line 3, even though pressure continues to elevate from vertical line 2 to vertical line 3 when tension actually decreases. This occurs because the volume (radius) becomes smaller and the wall thicker as the ventricle ejects. ED=end-diastolic, V=volume (or radius), WVT=wall thickness.

Aortic pressure
Left ventricular pressure
Left atrial pressure
Left ventricular volume
Left ventricular wall thickness
Left ventricular wall tension

After Wiggles

Elastance, change in pressure (ΔmmHg) for a given change in ventricular volume (Δml), indicates stiffness of the ventricle (ΔmmHg/Δml). A ventricle contracting feebly cannot generate great maximal elastance; one contracting forcefully can generate greater maximal elastance. As end-diastolic volume increases, elastance increases. Therefore, the intrinsic property of the ventricle to generate a contraction can be expressed as end-diastolic elastance (E_d) that expresses pressure-generating capability of the ventricle normalized to preload. The slope of the line connecting E_d.

LA
Ao
LV

LA
Ao
LV

Single P-V loop
Multiple P-V loops produced by Venous Occlusion.
Preload is decreased from red, to green, to orange.
What changes in function may predict morbidity and/or mortality:

As disappointing as it may be, except for changing QTc and/or QT instability, there are virtually no data available on what magnitudes of changes in any other parameter (e.g., heart rate, blood pressures, ejection fraction) have been able to predict insidious cardiotoxicity. Thus our mission is clear: animals (with or without disease, and possessing receptors which when activated/blocked result in insidious toxicity) must be exposed to test articles in a manner mimicking clinical uses. This is financially feasible if there is an animal model (with or without disease, that possesses receptors which when activated/blocked result in insidious toxicity) that ages within 9 months comparable to a human that might develop insidious toxicity in 18 years. An example: A 6 six year old child, given a course of doxorubicin, who develops cardiomyopathy when 18 years old, could be mimicked by a 1 month old sheep, given doxorubicin, and studied when it is 9 months old.....the human and the sheep would be immature when exposed and comparably mature at each step of evaluation..... age based upon, for example, known life span, hormonal status, bone structure, fecundity, and behavior.
IID

Compared to searching for toxicity occurring sooner, what are relative costs to predict insidious toxicity?

Although costs may vary enormously for many obvious reasons, a typical 30-day safety pharmacology study may cost $100,000, and a 90-day study may cost $150,000. So few safety pharmacology studies lasting longer than 30 or 90 days are performed, that a cost estimate will not be attempted. The reason that cost may not be linear with duration is because the following are relatively fixed costs: development of protocol, purchase of animals or instrumentation, analysis of spread sheets containing data for more time-points of recordings, computer and statistical analysis of parameters on sheets, whereas costs of prolonging a study are principally personnel, animal care, report-writing, and quality assurance.
doxorubicin

6 weeks old  9 months old

Putting Everything Together. II

I = E/R = (Q = ΔP/R); Q = [(ΔP • π • r⁴)/(8 • η • L)]; where: P = pressure, R = resistance, r = radius, η = viscosity
So who decides (in alphabetical order) what to do and how to do it; where do we go for advice?

- Administrators
- Clinical investigators
- Health care providers
- Individual intellectual curiosity
- Investors / clinical pharmacologists
- Patients / Subjects
- Pharmacologists / Physiologists / Safety Pharmacologists / Toxicologists
- Regulatory agencies
- Statisticians
Many thanks for your participation. We hope you found some value from our discussion. We’d be pleased to entertain comments and questions.
Thank you!

For a copy of this presentation, go to:

www.Battelle.org/Cardiotoxicity
http://www.toxicology.org/groups/ss/cvtss/announcement
s.asp