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Torsadogenic index: a proposal to improve survival rates in cardiac arrests due to prescribed drugs

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Since unexpected sudden deaths have been reported with the use of diverse non-cardiac drugs, cardio-safety experts focused their attention on security measures to improve survival rates in heart stoppages due to this prescribed drugs (Inchauspe, 2010a). Considering that prolongation of the QTc is a reliable marker of a menacing arrhythmia called torsade de pointes (TdP) – that can progress to ventricular fibrillation, application of Bazett, or Rautaharhu formulas can lead to a proper predictive valuation of a "torsadogenic risk." Case-analysis raises up the proposal that QTc or QTp will allow to identify high risk groups; performs a close pharmaco-vigilance and legally register ECG follow-up, avoiding unnecessary withdrawal of useful drugs from market.

Keywords: non-cardiac drugs, sudden death, torsadogenic risk, predictive evaluation, follow-up

INTRODUCTION

Sudden unexpected deaths from heart arrest have been reported with use of non-cardiac drugs since the early 1960s (Iyer, 2010). These drugs, which cause sudden death, have centered on torsade de pointes (TdP), a polymorphic ventricular arrhythmia that can progress to ventricular fibrillation and sudden death. Prolongation of the QTc interval is a surrogate marker for the ability of a drug to cause TdP. In individual patients an absolute QTc interval of >500 ms or an increase of 60 ms from baseline is regarded as indicating an increased risk of TdP. However, TdP can occur with lower QTc values or changes. Concern about a relationship between QTc prolongation, TdP, and sudden death applies to a wide range of drugs and has led to the withdrawal or restricted labeling of several. Arrhythmias are more likely to occur if drug-induced QTc prolongation coexists with other risk factors, such as individual susceptibility, presence of congenital long QT syndromes, heart failure, bradycardia, electrolyte imbalance, overdose of a QTc-prolonging drug, female sex, restraint, old age, hepatic or renal impairment, and slow metabolic status. Pharmacodynamic and pharmaco-kinetic interactions can also increase the risk of arrhythmias. The risk should be viewed in the context of the overall risks and benefits of anticancer treatment. It seems prudent, where possible, to select anticancer treatments that are not associated with marked QTc prolongation. If use of a QTc-prolonging drug is warranted, then measures to reduce the risk should be adopted.

L-Asparaginase is marketed as a drug for the treatment of acute lymphoblastic leukemia The main side effect is an allergic or hypersensitivity reaction; anaphylaxis is a possibility. No cardiac arrest effect has been observed before. However, in our clinical practice, a heart arrest was observed in a 1-year-old infant with leukemia.

EXAMPLE CASE

A male 1-year-old infant with Lymphatic acute leukemia was admitted in Hospital de Niños "Sor Maria Ludovica," in La Plata, Buenos Aires, Argentina. He received the following treatment:

Therapeutic protocol: IB protocol, MARMA Interfant-05

- Vincristine: 0.6 mg (push)
- Daunorubicin: 12 mg/kg
- L-Asparaginase: 1000 UI.

Particularly, after intravenously administering L-Asparaginase at the Hematology Ward, at 12:30 h the patient suffered cardiorespiratory arrest. Basic and advanced CPR techniques were initiated – endotracheal intubation and ambu ventilation, plus two doses of adrenaline and continued until the patient entered the Critical Care Unit about half an hour later. He presented hemodynamic decompensation (**Table 1**), hypothermia, and poor peripheral perfusion.

MATERIALS AND METHODS

Before a suspected diagnosis of an ANAPHYLACTIC OR IDIOSINCRATIC REACTION for this cardiac arrest, the child was treated as follows:

Basic and Advanced CPR (ILCOR) protocol

- Adrenaline (two doses).

Endotracheal intubation: respiratory Mechanical Assistance (RMA)

Setting: 1/fr = 22/VT 90/0.7 ri
VCV Mode: I:E = 1: 2.8.

Intravenous medications:

- H.P.: 60/2/1
- Colloid expansion: 10 mg/Kg
- Fentanyl: 1 gamma/kg/h
- Midazolam: 0.1 mg/kg/h

– Dopamine: 10 gamma/kg/min.

Hematological treatment:

K vitamin: 5 mg/dose/day.

After indicating the inotropic support and the volemia expansion by means of crystalloids, laboratory results were received. They confirmed hemostasis alteration, which is corrected by providing K vitamin (see **Table 2**).

RESULTS

Fortunately, this kid had a favorable evolution, as we can see in his tests controls (see **Table 3**).

In **Figure 1**, an ECG sample performed a day after the emergency is shown. It features a frequency of almost 200/min and P wave absence (only catching the last four beats), most presumably due to an inotropic effect.

Cardiac toxicity from these drugs is reported in *Goodman–Gilman´s Treatise.*

Individual idiosyncratic potential risk increases this danger in the whole of the protocol products (Litchner, 2010). Among them, both Vincristine and L-Asparaginase cause severe hepatotoxicity, derived from their pharmaco-kinetic metabolism, as was shown in the hemostasis defect.

The new decision of spreading the infusions of the protocol drugs within the week was made in order to allow the liver to recover (Swedborg, 2010).

The condition regressed completely at night (around 9:00 pm), and control parameters came back to normal (see **Table 2**).

Table 1 | Parameters I: hemodynamic decompensation.

Cardiac frequency	160/min
T.A.	48/32 mm Hg
O_2 sat.	100%
T°	36°C (hypothermia – coldness in distal extremities)
Peripheral perfusion	Capillary repletion > 3 s
Photomotor reflex	Isocoria – reactive pupillary reflex

Table 2 | Parameters II: hemostase impairment.

Prothrombin conc.	52%
KPTT	18.4 s
Partial thromboplastin time	86 s

Table 3 | Parameters III: recovery.

Cardiac rate	140/min
T.A.	82/55 mm Hg
O_2 sat.	100%
Respiratory rate	22/min
Peripheral pulses	Present

DISCUSSION

Currently, there are many products that can induce QT-interval prolongation at the ECG, thus favoring sudden death (Inchauspe, 2010b).

WHO defines Sudden Death as an episode appearing within 24 h of the beginning of an illness.

Under both eastern and western concepts, the combinations proposed in some protocols (and others enlisted by Dr. Wang (Wang, 2010) in the Harvard Office of Toxicology Exploration) could lead to a disruption of the ionic potassium channels of the myocardial cells (Asai, 2010), mostly in patients with congenital or acquired Long QT Syndrome. This condition could give rise to the appearance of precocious post-depolarizations (PDPs). Once they have reached a threshold amplitude, the PDPs can trigger highly risky arrhythmia known as "Torsade de pointes" (Dessertenne, 1966; Dessertenne et al., 1966), and a possible cardiac arrest.

Fortunately, today there is the possibility of carrying out ambulatory studies of cardiac frequency variability through continuous monitoring of spectral analysis of R–R′ (Inchauspe, 2011), corrected QT formulas are still a very practical way to determine QT-interval length next to the patient's bed:

Application of QTc (corrected) Bazett Formula:

$$\mathrm{QT(c)} = \frac{\mathrm{QT}}{\sqrt{R - R'}}$$

or QTp (precision) Rautaharhu Formula:

$$\mathrm{QT(p)} = \frac{656}{1 + \frac{\text{cardiac rate}}{100}}$$

Both formulas are appropriate as a QT screening since values over 0.45 s will be indicative of a QT-interval prolongation. And rates over 0.66 s would be likely to pose a torsadogenic risk (Lanzotti and Citta, 2003).

Proposal of a QTc or QTp screening will allow us to:

(a) Identify high risk groups;
(b) Perform close pharmaco-vigilance during treatment;

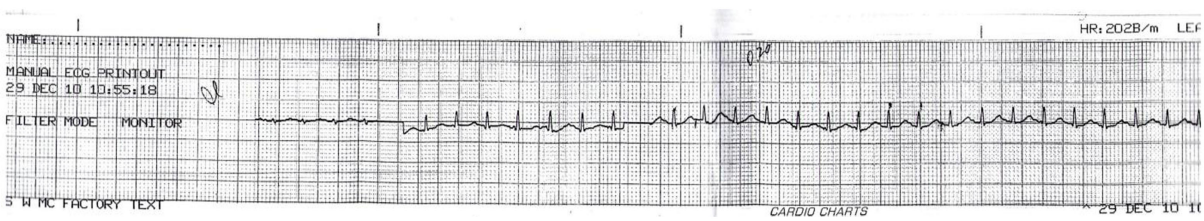

FIGURE 1 | ECG sample performed 24 hours after the emergency.

(c) Legally register ECG follow-up (useful as medical responsibility evidence);
(d) Avoid the unnecessary withdrawal of essential drugs from the market.

Each year 1,500,000 patients *severely injured by prescribed drugs* require hospitalization.

Out of these, 100,000 die, this being the fourth cause of death in USA.

Careful, long-term evaluation of cardiovascular safety can lead to better medical treatments.

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