Levosimendan in a case of severe peri-myocarditis associated with influenza A/H1N1 virus

Editor—Pandemic influenza A/H1N1 spread worldwide in 2009–2010, but several new cases have been identified in 2011 in Italy. Respiratory failure requiring mechanical ventilation was the hallmark during the influenza A/H1N1 pandemic and the patients with myocarditis were rare.1 2 We report the case of a fulminant peri-myocarditis associated with influenza A/H1N1 virus that was successfully managed with levosimendan.

A 54-yr-old female with case history of mild hypothyroidism developed flu with fever, cough, and weakness. Two days later, the fever disappeared but she was brought to the emergency department (ED) of our hospital because of severe constrictive thoracic pain and fainting. At ED admission, the patient was drowsy and hypotensive despite fluid infusion (crystalloids 1.5 litre). Electrocardiography showed sinus tachycardia, low-voltage QRS with inferior and septal ST elevation; cardiac troponin I (Tn) was 1.4 ng ml$^{-1}$ and procalcitonin (PCT) 0.37 ng ml$^{-1}$. Trans-thoracic echocardiogram (TTE) showed a global depressed left ventricular function (ejection fraction (EF) 35%) and mild periocardial effusion. After a thoracic CT scan to exclude an aortic aneurysm, the patient was admitted to our intensive care unit (ICU) still hypotensive and anuric. Cardiac index (CI) and blood $O_2$ saturation in the superior cava vein ($ScvO_2$) were very low. After a further fluid challenge, we started dobutamine (up to 8 $\mu$g kg$^{-1}$ min$^{-1}$) but arterial pressure, CI, and $cvO_2$ did not improve; serum lactate (La) and Tn increased to 5.5 mM and 3.9 ng ml$^{-1}$. Nasopharyngeal swab for reverse-transcriptase–polymerase-chain reaction (RT–PCR) test for the influenza A/H1N1 2009 virus resulted positive and, thereby, we started oseltamivir 150 mg twice daily and acetylsalicylic acid 3 g day$^{-1}$. The day after ICU admission, we performed cardiovascular magnetic resonance imaging that confirmed the diagnosis of severe peri-myocarditis (Fig. 1).

The persistence of hypotension and oliguria, associated with a mild pulmonary oedema and bilateral pleural effusion requiring non-invasive mechanical ventilation, led us to switch dobutamine to levosimendan (0.1 $\mu$g kg$^{-1}$ min$^{-1}$) before deciding on cardiovascular mechanical support. Twelve hours after levosimendan starting, CI increased, urine

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output improved (0.8 ml⁻¹ kg⁻¹ h⁻¹) and La decreased (3 mM). On ICU day 3, TTE revealed a significant improvement of EF (50%) and an increase in pericardial effusion. Tn increased to 11.2 ng ml⁻¹ and hypothesizing a persistence of A/H1N1 2009 virus, we performed a new RT–PCR test on nasal swab that was negative. In the following days, CI, ScvO₂, La, Tn, and urine output gradually improved and 6 days after ICU admission, the patient was transferred to the cardiac department and finally discharged home 12 days later with non-steroid anti-inflammatory drugs, diuretic, and β-blockers therapy.

Influenza A/H1N1 virus still caused death in Italy and worldwide in 2011, but the development of a peri-myocarditis associated with influenza A/H1N1 is still unusual. In our patient, the influenza A/H1N1 aetiology was likely because of clinical history, positive nasal swab RT–PCR test, and no identification of any other microbiological agents more commonly involved in severe peri-myocarditis. Patients' symptoms suggestive for cardiac disease during epidemic influenza must alert physicians on possible influenza A/H1N1 virus myocardial localization. Mechanical circulatory supports are reported as the main options to treat fulminant myocarditis in these patients. Moreover, in our patient, levosimendan may have played a cardioprotector role inhibiting apoptotic cell death and preventing cardiomyocyte loss, as previously reported in viral myocarditis in experimental models. Therefore, we believe that levosimendan can be considered as a therapeutic option in severe viral peri-myocarditis before the use of invasive mechanical circulatory supports.

Declaration of interest
None declared.

S. Busani
A. Pasetto
G. Ligabue
V. Malavasi
R. Lugli
M. Girardis*
Modena, Italy
E-mail: girardis.massimo@unimo.it

Do old pharmacokinetic parameter estimates predict new data?

Editor—Investigators may report different parameter estimates to describe the pharmacokinetics of a drug used in children. A number of parameter sets exist for describing propofol time–concentration data in children, often predicting quite different profiles in a typical child. These differences may be attributed to different patient populations, administration (single dose vs infusion), study duration, and differing analysis methodologies. Similarly, parameter sets for i.v. paracetamol are reported that differ.

An alternative to comparing predicted time–concentration profiles using differing parameter sets for a typical child is to ascertain if parameter estimates from an earlier study can predict concentrations similar to those reported in a new study is to use a modelling tool known as the visual predictive check. Concentration prediction intervals from an earlier study are graphically superimposed on those intervals determined from observed concentrations in the new study. Simulation is performed with parameter estimates from the earlier study using 1000 subjects with characteristics taken from new patients. For data such as these where covariates such as dose, weight, and height are different for each patient, a prediction-corrected visual predictive check is used; observations and simulations are multiplied by the population baseline value divided by the individual-estimated baseline. Figure 1 shows a graphical representation. The median predictions and observations graphically lie on top of each other. Observed concentration intervals are narrower than predictions, reflecting limited subjects (n = 33) in the new study.

The earlier study (n = 144) was performed using a prodrug of paracetamol (procetamol) that is rapidly metabolized to paracetamol (F = 0.5) by plasma esterases. This graphical validation supports parameter estimates for i.v. paracetamol determined using the prodrug.

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B. J. Anderson1*
J. McLay2
K. Allegaert3
T. Engelhardt2
1Auckland, New Zealand
2Aberdeen, UK
3Leuven, Belgium
*E-mail: briana@adhb.govt.nz

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Fig 1. Prediction-corrected visual predictive check using parameter estimates from an earlier study and observations from the new study. All plots show the median and 90% intervals (solid and dashed lines). (A) shows all prediction-corrected observed concentrations. (A) shows prediction corrected percentiles (10%, 50%, and 90%) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (green-shaded areas).