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Stability of sildenafil (Revatio®) dilutions in dextrose 5%

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Dear Editor,

With great interest we read the paper of Fraisse et al. [1] in which the authors document the intravenous (i.v.) use of sildenafil in paediatric patients with congenital heart disease and pulmonary hypertension. The findings of the authors are important, since the commercially available sildenafil solution for injection (Revatio® 0.8 mg/ml, 50 ml) is only licensed for administration as a bolus injection and unwanted excessive hypotensive effects may occur after administration of a bolus dose. Recently, we administered sildenafil intravenously to two paediatric patients at the Erasmus MC Sophia Children's Hospital. One of the children (girl, age 4.5 years, 17 kg) was treated with sildenafil orally for 16 days (3 mg/kg daily) and subsequently with sildenafil i.v. bolus injections for 27 days (0.5–1.0 mg/kg three times daily). Bolus sildenafil injections resulted in reductions in arterial systolic and diastolic pressures of approximately 20%. The second child (boy, neonate, age 23 days, 3.0 kg) received one bolus sildenafil i.v. dose of 0.2 mg/kg, after which arterial systolic and diastolic pressures dropped also by approximately 20%. Thereafter, a sildenafil continuous infusion was started with a loading dose of 0.4 mg/kg in 3 h and maintenance dose of 1.9 mg/kg daily for 5 days in total. During the continuous i.v. infusion, no marked fluctuations in arterial systolic and diastolic pressures were observed.

As described by Fraisse et al. [1], maintenance infusions of sildenafil may have clear advantages. However, in order to correctly administer continuous i.v. (maintenance) infusions of sildenafil to paediatric patients, the commercially available product may frequently require dilution prior to administration. The current authorized version of the summary of product characteristics of Revatio®, and major handbooks such as those by Trissel [2] and Bing [3], as well as other pharmaceutical literature sources, do not provide information on how sildenafil dilutions for continuous i.v. administration should be prepared and stored. Also Fraisse et al. [1] did not explicitly state how the maintenance infusion should be prepared and stored.

To address this issue, we studied the stability of two Revatio® dilutions (0.067 and 0.667 mg/ml) in dextrose 5%, which is the diluent of choice in most neonatal and paediatric intensive care units. Both dilutions were stored in 50-ml Luer-Lok™ polypropylene syringes (BD Plastipak, Spain) at ambient room temperature (20–25°C) and at 37°C (laboratory incubator) for 24 h and 7 days. Thereafter, and after performing a system suitability test and the preparation of two three-point aqueous calibration curves (concentration ranges are 0.04–0.08 and 0.4–0.8 mg/ml), we determined the concentration of sildenafil in both dilutions using a validated HPLC method (C18 ODS-3 5-μm column, 50:50 v/v acetonitrile/ammonium acetate 10 mM mobile phase, detection at 292 nm; Shimadzu LC20 diode array detector and HPLC system), and the coefficients of variation for repeatability, reproducibility and accuracy were found to be 0.1, 1.7 and 1.8%, respectively. The system suitability test complied with the general requirements of the United States Pharmacopeia [tailing and capacity (k') factors were about 0.97 and 3.3, respectively]. The calibration curves exhibited satisfactory correlation coefficient and goodness-of-fit values (both $\geq$0.999).

Measurement of the sildenafil concentrations in both dilutions at the end of the incubation periods (1 and 7 days) suggested no marked degradation at either temperature (room temperature or 37°C), since all of the concentrations measured were higher than 95.4% (percent of nominal concentration at $t = 0$ h) and since the peak-purity index was 1.000 in all of the measurements, indicating the absence of degradation products.

Our findings therefore suggest that Revatio® dilutions in dextrose 5% in the range 0.067–0.667 mg/ml are chemically stable for up to 1 week at room temperature (and hence clinically usable provided that antiseptic conditions are strictly applied during compounding). Our findings thus provide the pharmaceutical basis to enable administration of diluted sildenafil as a maintenance infusion to paediatric patients.

References

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