Implications of new recommendations about Sildenafil in children with PAH. Is reduction of Sildenafil to recommended doses safe?

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Introduction: Sildenafil has been used off-label for treatment of PAH in the paediatric population, however data on dosing has been limited. A recent extension to a randomised control trial of sildenafil in children with PAH (STARTS – 2) reported an unexplained excess mortality in patients randomized to higher doses. Consequently the European Medicines Agency (EMA) recommended children weighing 8 - 20kg should be treated with 10mg three times a day and patients weighing 20kg or more should be treated with 20mg three times a day. We sought to assess the clinical impact and safety of reduction of Sildenafil to the recommended doses.

Methods: Twenty-three patients (11 females) with median age 9.2 (range 1.2 – 15.4) years were included. PAH was idiopathic in 7, associated with lung disease in 9, associated with congenital heart disease in 5. Ten patients were on monotherapy with Sildenafil and 13 patients were combination therapy. Nine patients weighed < 20kg requiring mean reduction of 18.7 mg (range 10-45) sildenafil per day; 14 patients weighed > 20kg requiring mean reduction of 43 mg (range 20-100). Patients were assessed prior to reduction of dose and after reduction with median time interval of 13 weeks (IQR 10-17).

Results: No additional PH treatment was required during the weaning period. Following dose reduction 3 patients improved functional class, 2 worsened, there was no change in functional class in the remainder. No patient was in functional class IV and there were no episodes of syncope.

There was no significant fall in six-minute walk distance (mean(SD) baseline distance 414(56)m, at follow-up 412(40)m; mean change -2.5(92), p= 0.88).

On MRI (n=5) there was no significant change between baseline and follow-up in RVEDV (mean RVEDV= 77ml/m2 and 83.6ml/m2 respectively, p-value=0.58), RVESV (mean RVESV= 32.8ml/m2 and 39ml/m2 respectively, p-value= 0.0579) or RVEF (mean RVEF 56.8 % and 53.6 % respectively, p-value= 0.1)

Conclusion:
These early data may support physicians trying to implement the new dosing recommendations into clinical practise. However, close monitoring for clinical deterioration remains paramount for this progressive disease.