Therapeutics Today

May 2018
Number 5

New guidance on Lyme disease. Lyme disease is a tick-borne infectious disease, caused by different species of *Borrelia*. It is transmitted to humans through a bite from an infected tick. Most bites do not transmit the disease; infection is more likely the longer a tick is attached to the skin, therefore prompt, correct removal of the tick reduces the risk of transmission. Ticks live in grassy and wooded areas, both in rural and urban locations; people who spend time in these areas (for work or recreation) are at increased risk of tick exposure. Lyme disease occurs mainly in the northern hemisphere, therefore travellers to certain areas of Europe and North America may be at risk. The true incidence of Lyme disease is unknown; the overall mean prevalence of *B. burgdorferi* in Europe has been estimated at about 12%, with the highest tick infection rates located in central Europe, including Austria, Czech Republic, southern Germany, Switzerland, Slovakia and Slovenia. **Clinical presentation**: Infection may go unnoticed but if symptoms occur it is known as Lyme disease. Up to 90% of patients with an acute infection may develop a rash "erythema migrans" at the site of the tick bite (1 to 4 weeks post bite), which may be mistaken for cellulitis. Flu-like symptoms may also be present. Neuro-borreliosis is the **main complication** (seen in about 10% of cases, usually within 6-12 weeks of the initial infection). It can present as facial palsy, lymphocytic meningitis or radiculoneuritis. Presentations of **late Lyme disease** can affect the skin, nervous, cardiac or musculoskeletal systems. **NICE has recently published guidance on Lyme disease** which outlines the need for increased awareness of Lyme disease and provides recommendations on its diagnosis (using clinical and laboratory testing) and antibiotic treatment, appropriate to the stage and site of disease. Doxycycline (for up to 21 days) is the treatment of choice in the acute stage. Longer courses may be needed for manifestations such as arthritis or skin involvement. IV ceftriaxone is recommended for neuroborreliosis. The full guideline is available at: **www.nice.org.uk/guidance/ng95/resources/lyme-disease-pdf-1837756839877.** [Editor's note: the Health Protection Surveillance Centre (**HPSC**) has a useful webpage on Lyme disease, which contains information on *Borrelia* infection, a diagnostic toolkit for erythema migrans and guidance on management of Lyme disease: **www.hpsc.ie/a-z/vectorborne/lymedisease/informationforhealthcareprofessionals/**]

Congenital malformations with different antiepileptic drugs. A recent cohort study compared the risk of major congenital malformations (MCM) with 8 commonly used antiepileptic drugs (AED) used as monotherapy: carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproate (***Lancet Neurol 2018; doi: 10.1016/S1474-4422(18)30107-8.***). The EURAP (European and International Registry of Antiepileptic Drugs in Pregnancy) registry was used to identify pregnancies (n=7355) exposed to one of the 8 AED between June 1999 and May 2016. The **primary endpoint** was risk of MCM at one year after birth. **Results** showed a prevalence of MCM of 74/2514 (2.9%) for lamotrigine, 107/1957 (5.5%) for carbamazepine, 142/1381(10.3%) for valproate, 17/599 (2.8%) for levetiracetam, 10/333 (3%) for oxcarbazepine, 19/294 (6.5%) for phenobarbital, 6/152 (3.9%) for topiramate and 8/125 (6.4%) for phenytoin. Multivariate analysis showed that **MCM was significantly higher for all doses of valproate and carbamazepine, as well as for phenobarbital at doses of >80mg/day**. The risks of MCM associated with lamotrigine, levetiracetam and oxcarbazepine were within the range reported in the literature for offspring unexposed to AED; data for topiramate and phenytoin were based on small numbers of exposure in this cohort, therefore these results should be interpreted with caution. The authors conclude that the findings may facilitate rational selection of AED monotherapy during pregnancy.

New restrictions on use of valproate (Epilim®). Valproate is known to have a high teratogenic potential (**30-40% risk of developmental disability and a 10% risk of birth defects**). In 2014, additional warnings and restrictions were introduced to minimise these risks of use in women of childbearing potential (WOCP). The EU Pharmacovigilance Risk Assessment Committee (PRAC) recently assessed the impact of these restrictions in reducing exposure to valproate use during pregnancy, following concerns about their effectiveness. Following that assessment, PRAC has recommended that **important new contraindications** be introduced for valproate use and has **strengthened warnings and measures** (including the introduction of a **pregnancy prevention programme**) to further prevent valproate exposure during pregnancy; these are now being implemented in Ireland by the marketing authorisation holder for Epilim®, Sanofi, in conjunction with the HPRA.

The following advice has been circulated to healthcare professionals (HCPs):

- HCPs should ensure **that patients are made aware that in Ireland the brand name of valproate is Epilim®.**
- A **Valproate Pregnancy Prevention Programme** is being implemented nationally and across the EU; valproate should only be prescribed and dispensed in accordance with this programme.
- In pregnancy and in WOCP **new contraindications** apply:

    - **Valproate is contraindicated in WOCP, unless all the conditions of the pregnancy prevention programme are met**
    - **In epilepsy**, valproate is contraindicated in pregnancy unless there is no suitable alternative treatment
    - **In bipolar disorder**, valproate is contraindicated in pregnancy
    - If used in female children or WOCP, valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder

- For WOCP currently using valproate, prescribers should re-evaluate treatment to ensure that the conditions of the pregnancy prevention programme are met and that valproate remains the most appropriate therapeutic option for them.
- **Updated educational materials (a patient guide, a HCP guide and an annual risk acknowledgment form) will be distributed in paper form to HCPs shortly by the marketing authorisation holder for Epilim® following approval by the HPRA.**
- **Prescribers** should discuss the risk with their patients and ensure that relevant patients receive and understand the patient guide.
- **Pharmacists** should ensure that relevant patients are aware of and understand the risk and provide them with the package leaflet and a patient card every time valproate is dispensed

The **Valproate Pregnancy Prevention Programme** is a detailed plan involving the precautions to be taken when considering use of valproate in female children and WOCP. Information on the need for comprehensive education prior to the initiation of treatment, pregnancy testing, use of effective contraception, annual treatment reviews, pregnancy planning for WOCP and what to do in case of pregnancy are clearly described. Further details on the pregnancy prevention programme and updated educational materials will be available from **www.hpra.ie** or **www.sanofi.ie.**

NMIC enquiry answering service survey. The NMIC would like to thank all those who have responded to date to our anonymous enquiry answering service survey. **The survey will be ongoing until the end of June**. The results of the survey will be published in a future TT newsletter.

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. References are available on request. This ***newsletter is produced by the National Medicines Information Centre, St. James's Hospital (SJH) Dublin 8 and Dept of Therapeutics Trinity College, Trinity Centre, SJH.*** *Tel: Direct Line (01) 473 0589 or 1850 727 727 Email: nmic@stjames.ie*