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Sheep dips, organophosphates and the alleged activities of Russian agents

We open this issue with an article which may become far more topical even than was originally intended. David Mantle and Iain Hargreaves discuss organophosphate poisoning and its treatment. This was originally written primarily with respect to sheep farmers and poisoning by organophosphate-based sheep dips, but with this year's events in Salisbury, concerning the poisoning of the Skripals, and with various speculations about the alleged activities of Russian agents, this may assume an even more serious importance for health care.

Ria Bhola and Fiona Greenwood have news for us on some very interesting developments in the field of migraine treatment and prevention; this is a common neurological disorder that is extremely disabling and often misunderstood. A possible treatment with new monoclonal antibodies would, of course, be extremely welcome.

In the BANN pages, Emily Spence reports on the 47th Annual BANN conference and tells us about the forthcoming 11th EANN Quadrennial Congress and SBNS Spring Meeting in Manchester.

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In their regular columns, Sarah Mehta reports on a new video guide to understanding the symptoms of Parkinson's, a subject touched on so briefly during professional training; and Sue Thomas tells us about the NHS 10-year plan, which has been described by former health and social care secretary, Jeremy Hunt, as one of the 'big moments in NHS history'.

There is the usual Research Roundup from John Costello, reviewing recent publications. And Teresa Leahy and Timothy J Counihan write on physician and advanced nurse practitioner (ANP) decision-making in the management of multiple sclerosis. They conclude that diagnostic and management decision-making by the ANP for patients with potential relapses and/or treatment escalation is on a par with that of the neurologist.

To conclude, Sarah Jane Palmer, in her regular column, writes a thought-provoking piece on the neuroscience of meditation.

This issue also features a stroke supplement, and in the foreword, Bev Bennett heralds a possible 'golden age' for stroke rehabilitation. The supplement leads with an article on the 'York triage, treat and transfer' model of stroke care, a report on the rationalisation of stroke care in North Yorkshire. An inspiring tale of the culture of continuous improvement.

Amanda Jones and Bev Bennett write on rekindling the community stroke rehabilitation unit; and we have a fascinating article by Lucinda Jarrett on a performance arts model for neurological rehabilitation. Why should we not think 'outside the box' a little? BJNN

Brian Cooper, Editor

Organophosphate poisoning and coenzyme Q10: an overview

David Mantle and Iain P Hargreaves

ABSTRACT

Organophosphate (OP) poisoning can occur in acute and chronic forms. In developing countries, both forms are common, and represent a major cause of morbidity and mortality. In the UK, organophosphate poisoning is most likely to be encountered in chronic form, with sheep farmers the section of the population at greatest risk. The problem of poisoning in sheep farmers caused by exposure to organophosphate-based sheep dips has become increasingly apparent. Symptoms include fatigue, muscle pain and neurological problems. There is no specific treatment for this condition. OP toxicity is classically associated with inhibition of acetylcholinesterase enzymes involved in the process of neurotransmission. However, there is evidence that OP poisoning can also cause mitochondrial dysfunction, compromised cellular energy supply, oxidative stress and inflammation. Symptoms of sheep dip poisoning correspond with those known to result from depletion of coenzyme Q10 (CoQ10), a vitamin-like substance with a key role in cellular energy generation within mitochondria, as well as antioxidant and anti-inflammatory action. The authors have therefore reviewed evidence that oral supplementation with CoQ10 may provide effective symptomatic relief for farmers suffering from OP sheep dip poisoning. Evidence in support of the above is presented for: (a) OP-induced mitochondrial dysfunction; (b) beneficial effects of CoQ10 administration following OP exposure in relevant animal models; and (c) evidence from clinical studies in human subjects. The dosage of CoQ10 proposed (100 mg three times daily) is based on that required to raise blood levels to at least 3 µg/mL, which has been shown to be a requirement to effectively counter CoQ10 depletion in other disorders, particularly heart disease. It is important to note that a CoQ10 supplement with appropriate documented bioavailability should be used, since poor bioavailability may have been responsible for the failure of some previous studies. The safety of CoQ10 supplementation has been confirmed in more than 200 randomised controlled clinical trial studies on a wide range of disorders. In addition to the above, because of the increased risk of the use of OP compounds in terrorist-type poisoning incidents in the UK, a brief discussion on the management of acute OP poisoning is included.

Key Words coenzyme Q10; organophosphate poisoning; mitochondrial dysfunction; oxidative stress

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Organophosphate (OP) compounds are toxic synthetic compounds, commonly derived from esters of phosphoric acid, and with the general structure $P(=O)(OR)_3$, where 'R' represents the functional group (Rathnayake and Northrup, 2016). OPs are used as pesticides and herbicides, and include the compounds, parathion, chlorpyrifos, diazinin and dichlorvos (Kazemi et al, 2012). Organophosphate (OP) poisoning can occur in acute or chronic forms, both of which are common in developing countries (Sinha and Sharma, 2003). In the UK, OP poisoning is less common, and most likely to occur in chronic form. Specific sections of the UK population for which OP poisoning is of relevance include military personnel (Gulf War syndrome) (White et al, 2016), aircraft cabin crew (Schindler et al, 2013) and agricultural workers (particularly sheep farmers).

The problem of sheep dip poisoning in farmers has become increasingly apparent, as evidenced by parliamentary debate and subsequent demands for a public enquiry (Hansard, 2015). The problem arose from the compulsory use of OP-based sheep dip products against external sheep parasites such as scab mites, particularly during the 1980s. It has been estimated that in 1988, for example, this involved twice-yearly dipping of some 40 million sheep by the UK's 95 000 sheep farmers. This required total immersion of the sheep in the pesticide, usually with considerable splashing, and often with inadequate protective clothing. There was also a health risk from handling the sheep dip in concentrated form, which could contain up to 60% by weight of commonly used active agents, such as diazinon (Buchanan et al, 2001).

OP pesticides are effective by targeting enzymes involved in nerve transmission in insects (i.e. via acetylcholinesterase inhibition); although these pesticides are selected on the basis of their specific chemical structures to target particular insect pests, they can also exhibit toxicity in higher organisms via the same mechanism. Exposure to sheep dip, via skin contact or inhalation, has resulted in some farmers developing chronic health problems. Symptoms typically include fatigue, muscle pain and neurological problems, including cognitive impairment. Evidence of neurological abnormalities in sheep farmers exposed to OP pesticides was reported by Beach et al as early

as 1996. There is no effective therapy for the treatment of farmers with sheep dip poisoning. In this article, the authors have therefore reviewed evidence that oral supplementation with the vitamin-like substance coenzyme Q10 (CoQ10) may provide effective symptomatic relief in farmers suffering from chronic OP sheep dip poisoning.

Coenzyme Q10

CoQ10 is a vitamin-like substance that plays a key role in the biochemical process within mitochondria, which supplies all cells with the energy required for their normal functioning; this is of particular importance in tissues with a high energy requirement, such as the heart, skeletal muscles and brain (Mantle, 2015). CoQ10 functions in energy generation by serving as an electron carrier in the mitochondrial respiratory chain (MRC) which generates adenosine tri-phosphate (ATP), the energy currency of the cell, by the process of oxidative phosphorylation (Hargreaves, 2003). CoQ10 is also important as a lipid soluble antioxidant, protecting cells (and particularly mitochondria) from the potentially damaging effects of toxic free radical species (oxidative stress) generated during normal cellular metabolism. In addition, CoQ10 has been shown to directly affect the expression of a number of genes, including some of those involved in inflammation. An adequate supply of CoQ10 is essential for normal functioning of mitochondria. Although some CoQ10 is obtained from the normal diet (approximately 5 mg/day), most of the daily CoQ10 requirement (estimated at 500 mg) is synthesised within the body. As people age, the capacity of the body to synthesise its own CoQ10 decreases; optimal production occurs around the mid-twenties, with a continual decline in tissue levels thereafter.

Neurological effects of OP poisoning

The inhibition of acetylcholinesterases, enzymes that serve to terminate synaptic transmission by breakdown of the neurotransmitter acetylcholine, following OP exposure, can affect both the central and peripheral nervous system, causing muscle weakness, seizures and respiratory failure, as well as salivation, nausea, anxiety and confusion. These symptoms develop shortly after acute exposure, and may require emergency medical treatment, typically resolving over a period of several days. In the longer term, inhibition of an additional enzyme, neuropathy target esterase, may result in axonal degeneration and development of peripheral neuropathy several weeks after initial exposure. In addition to the inhibition of the above enzymes, mitochondrial dysfunction, oxidative stress and inflammation, as described in the following section, may result from OP exposure, with long-term neurological consequences. Exposure to OP pesticides has been implicated in the pathogenesis of neurodegenerative disorders such as Parkinson's disease and amyotrophic lateral sclerosis (Sanchez-Santed et al, 2016; Chuang et al, 2017). In addition, OP poisoning has been reported to result in poorer performance in standardised neuropsychological tests, and an increased risk of developing psychiatric disorders (Jaga and Dharmani, 2007; Stallones and Beseler, 2016).

Mechanism of OP toxicity

OP toxicity in humans is classically associated with the irreversible inhibition of acetylcholinesterase enzymes involved in the process of neurotransmission. Accumulation of acetylcholine at nerve endings results in over-stimulation of muscarinic and nicotinic receptors, resulting in the neurological symptoms described above. The reduction in accumulated acetylcholine and reactivation of acetylcholinesterase is targeted via conventional antidote treatment with atropine and oximes, following acute poisoning (Bairacharya et al, 2016). However, other factors may be involved; there is evidence that pesticide poisoning in general, and OP poisoning in particular, causes disruption of cellular energy production within mitochondria, oxidative stress and inflammation (Pearson and Patel, 2016; Vanova et al, 2018). Oxidative stress following OP exposure has been demonstrated both in vitro (Ramirez-Vargas et al, 2017; Deeba et al, 2017) and in vivo (Paul et al, 2016; Zepeda-Arce et al, 2017), via quantification of stable biochemical markers of oxidative damage such as malondialdehyde (a marker of lipid damage) and 8-hydroxydeoxyguanosine (a marker of DNA damage) (Wang et al, 2016; Ramirez-Vargas et al, 2017).

Symptoms of OP poisoning correspond with those known to result from depletion of CoQ10, which include muscle weakness, fatigue and neurological impairment (Hargreaves, 2003). The plausibility of a role for CoQ10 supplementation in OP poisoning is based on the following: i) the key role of CoQ10 in the process of mitochondrial cellular energy production; ii) the role of CoQ10 as a potent lipid-soluble antioxidant; iii) the role of CoQ10 as an anti-inflammatory mediator; iv) the role of CoQ10 as a mediator of paraoxonase activity (paraoxonase enzymes are responsible for the degradation of organophosphates). In addition, there is evidence from animal model studies that administration of CoQ10 can reduce pesticide-induced mitochondrial dysfunction.

We have therefore reviewed evidence from i) to iv) above that oral supplementation with CoQ10 may provide effective symptomatic relief in farmers suffering from OP sheep dip poisoning.

Evidence supporting CoQ10 supplementation in OP poisoning

The first part of the evaluation is concerned with evidence for OP-induced mitochondrial dysfunction. A number of studies in cell culture or animal model systems have identified OP-induced mitochondrial dysfunction. These include the effects of mevinphos in PC12 cells (Chan et al, 2006), chlorpyrifos in hens

(Salama et al, 2014) or rats (Basha et al, 2014), and dichlorvos in rats (Kaur et al, 2007; Masoud et al, 2009; Binukumar et al, 2010). In the above studies, mitochondrial dysfunction was identified in terms of altered activity of mitochondrial enzymic complexes I to IV, decreased electron transport and ATP production, and increased free radical generation resulting in oxidative stress following mitochondrial exposure to organophosphates. In cultured rat neurons, Middlemore-Risher et al (2011) found exposure to chlorpyrifos resulted in altered mitochondrial number, morphology and transport.

The second part of the evaluation is concerned with pre-clinical evidence for beneficial effects of CoQ10 administration following OP exposure. CoQ10 is an essential cofactor of enzyme complexes involved in the biochemical process supplying all cells with energy. Specifically, CoQ10 is an intermediate in the electron transport system that generates energy in the form of ATP, shuttling electrons from complexes I and II to complex III of the mitochondrial respiratory chain (Hargreaves, 2003). CoQ10 is also important as a major fat-soluble free radical scavenging antioxidant, protecting cell membranes (particularly those of the mitochondria) from free radical-induced oxidative damage. Deficiency of CoQ10 has been implicated in a variety of disorders, including cardiovascular, musculoskeletal and neurological diseases (Hargreaves, 2003).

Binukumar et al (2011; 2012) demonstrated that administration of CoQ10 reduced free radical generation, improved mitochondrial complex I–IV activity and mitochondrial function in brain tissue of rats exposed to dichlorvos, as well as improving cognitive performance. CoQ10 administration reversed depressed mitochondrial respiratory enzyme activities in brain tissue of rats exposed to mevinphos, increasing them to control levels (Li et al, 2005; Yen et al, 2005). CoQ10 in both nanoparticular and non-particular forms demonstrated hepatoprotective activity against dichlorvos (Eftekhari et al, 2018). In rabbits, administration of CoQ10 significantly improved acetylcholine activity and reduced cardiac tissue peroxidation following acute exposure to the OP dichlorvos (Bayir et al, 2013). In an in vitro study using human lymphocytes exposed to chlorpyrifos, Ghayomi et al (2016) reported that acetylcholinesterase activity was increased and oxidative stress markers reduced following administration of CoQ10.

With regard to clinical evidence, relatively little work has been carried out to evaluate the potential benefit of CoQ10 administration in human subjects exposed to organophosphates. Evidence for mitochondrial dysfunction and impaired ATP generation in patients with Gulf War syndrome, obtained via ^{31}P magnetic resonance spectroscopy, was described by Koslik et al (2014). Golomb et al (2014) subsequently reported that supplementation with CoQ10 (300 mg/day for 3 months) significantly improved symptoms and physical functioning in a randomised, double-blind, controlled trial of 46 Gulf War veterans. Gulf War syndrome presents with symptoms of chronic fatigue, musculoskeletal pain and neurological issues, resulting from OP exposure due to uniform impregnation, etc. Gulf War syndrome is arguably the closest parallel to pesticide poisoning in sheep farmers (White et al, 2016).

The question arises as to why farmers should show differing susceptibility to OP poisoning (i.e. other than the extent of exposure). This has been linked to polymorphisms in the activities of the paraoxonase enzymes, which detoxify organophosphates or their active metabolites in blood or other tissues (Costa et al, 2013; You et al, 2013). Exposure to organophosphates reduces paraoxonase activity (Medina-Diaz et al, 2017). Decreased paraoxonase activity has been linked with impaired mitochondrial function (Devarajan et al, 2011), and paroxonase polymorphisms have been identified in farmers suffering ill health following sheep dip exposure (Cherry et al, 2002; Mackness et al, 2003; O'Leary et al, 2005; Cherry et al, 2011; Costa et al, 2015).

In addition to its role in mitochondrial energy production, CoQ10 supplementation has been reported to increase paraoxonase activity (Bruge et al, 2012; Ahmadvand et al, 2014). The capacity of the body to synthesise its CoQ10 requirement decreases with age; optimal production occurs around the mid-twenties, with a continual decrease thereafter. Older farmers with a polymorphism for reduced paraoxonase activity may therefore be at particular risk of OP poisoning.

On the basis of the evidence presented above, we therefore suggest that supplementation with CoQ10 may significantly benefit symptoms of OP poisoning in sheep farmers, via improvement in mitochondrial function; specifically increased respiratory chain enzyme activity, increased ATP production and reduction in free radical-induced oxidative damage to mitochondria. In addition, CoQ10 supplementation may increase residual levels of paraoxonase, which may further help to counter the adverse effects of OP exposure. The proposed dosage would be 100 mg three times daily, to be taken indefinitely. The proposed dosage is based on that documented to raise blood CoQ10 levels to at least 3 µg/mL (Weis et al, 1994), which in turn has been shown to be a requirement to counter CoQ10 depletion in other disorders, particularly heart failure (Mantle, 2015).

With regard to heart function, both acute and chronic exposure to OP pesticides has been linked to an increased risk of developing cardiovascular disease. This may be manifest as cardiac arrhythmia, atherosclerosis or hypertension (Karki et al, 2004; Hung et al, 2015; Samsuddin et al, 2016). Increased risk of cardiovascular disease following OP exposure may be linked to reduced paraoxonase activity, since paraoxonase has been recognised as an anti-atherogenic enzyme (Mahrooz, 2016; Chistiakov et al, 2017).

Requirements for coenzyme Q10 supplementation

CoQ10 is a lipid-soluble substance absorbed from the digestive tract in the same manner as other dietary fats. Because of its hydrophobicity and large molecular weight, absorption of CoQ10 is in general slow and somewhat limited. Oil-based formulations show highest bioavailability. Absorption of CoQ10 is non-linear, with increasing doses absorbed to a decreasing degree. CoQ10 is therefore best administered in split doses (typically 100 mg two or three times daily).

When first manufactured, CoQ10 is produced in a crystalline form which cannot be absorbed from the digestive tract. In CoQ10 supplements, this crystalline form must be further treated to break it down into individual molecules to enable absorption, and most importantly crystals should not re-form within the capsule. Supplement manufacturers vary in their ability to fulfil these requirements, and previous clinical trial studies reporting lack of benefit in a variety of disorders may have failed because of insufficient dosage and/or lack of bioavailability of the particular supplement used.

Safety of coenzyme Q10 supplementation

The safety of CoQ10 has been assessed by Hidaka et al (2008) and Hosoe et al (2007). CoQ10 is generally well tolerated, with no serious adverse effects reported in long-term use. Very rarely, individuals may experience mild gastrointestinal disturbance. There are no known toxic effects, and CoQ10 cannot be overdosed. CoQ10 is well tolerated in healthy adults at an intake of 900 mg/day, and in rats at a dose of up to 1200 mg/kg/day. In addition, Yamaguchi et al (2009) reported that CoQ10 had no genotoxic activity. CoQ10 is not recommended for pregnant or lactating women, in whom the effects of CoQ10 have not been extensively studied. The safety of CoQ10 has been confirmed in more than 200 randomised controlled trials, on a wide range of disorders.

Nursing implications

The role of the nurse in the management of patients with chronic OP poisoning is essentially three-fold:

- To be able to recognise the symptoms of chronic OP poisoning at the initial patient presentation. Individuals with long-term symptoms of fatigue, muscle pain or nerve damage (e.g. paraesthesia), with an agricultural background (particularly sheep farmers), should be questioned as to their previous exposure to sheep dip or related chemicals. Reduced activity of acetylcholinesterase in plasma or red cells is indicative of OP exposure.
- There is no satisfactory conventional treatment for chronic OP poisoning. Nurses should therefore be aware of the potential use of oral CoQ10 supplementation to provide symptomatic relief for patients with chronic OP poisoning, based on evidence presented in this review article.
- To be able to provide relevant information to the patient and relatives about OP poisoning, given the general lack of knowledge within the medical profession regarding this disorder.

As noted above, under normal circumstances acute OP poisoning rarely occurs in the UK, compared to its chronic form equivalent. However, given the increased risk of terrorist attacks within the UK, and the probability of OP agent involvement (Tanimoto et al, 2017), a brief description of the nursing implications has been included in this review. Both the nerve agent used in the recent Salisbury poisoning incident (novichok) (Harding et al, 2018), and that used in the Tokyo subway attack in 1995 (sarin) (Pletcher, 1995), are organophosphate compounds. It should be noted that the organophosphate compounds in sheep dip or other insecticides are present at substantially lower levels than those comprising substances such as novichok or sarin.

Acute OP poisoning is a medical emergency, typically requiring intensive care. Diagnosis is made on the basis of patient history and characteristic symptoms, including pupil myosis, rapid respiration, bronchospasm, salivation, muscle tetany and coma. Initial symptoms may vary according to the route of exposure (respiratory, dermal or gastrointestinal), although similar clinical presentation will eventually result. OP poisoning can result in over-stimulation of both muscarinic and nicotinic receptors. Most symptoms of OP poisoning result from excessive muscarinic receptor stimulation Management comprises respiratory and cardiovascular support, administration of specific antidotes such as the muscarinic antagonist atropine, and decontamination of the skin or gastrointestinal tract (e.g. via induced vomiting or use of activated charcoal), as appropriate.

Respiratory dysfunction and pulmonary oedema is a leading cause of death in acute OP exposure. Atropine competes with acetylcholine for post-synaptic muscarinic receptors, thereby negating the clinical effects resulting from accumulated acetylcholine following OP exposure. The typical atropine dosage used is 2–4 mg intramuscular, given at intervals of approximately 5–10 minutes until symptoms have abated. It is important that antidotal therapy is given as quickly as possible, while OP-induced acetylcholinesterase inhibition is still reversible (typically several hours, depending on OP type). It should be noted that atropine counters symptoms resulting from the over-stimulation of muscarinic receptors, but not those resulting from over-stimulation of nicotinic receptors.

The risk of nosocomial poisoning to medical staff when dealing with acute OP poisoning cases should be considered (Stacey et al, 2004). Patient decontamination should therefore be undertaken as soon as practicable, using soap and water or aqueous 0.5% hypochlorite solution (Collombet, 2011).

KEY POINTS

- Organophosphate (OP) poisoning can occur in acute or chronic forms, the treatments for which are radically different
- In the UK, chronic OP poisoning is most likely to be encountered in agricultural workers (particularly sheep farmers)
- Acute OP poisoning is most likely to be encountered following terrorist attacks using so-called nerve agents
- Acute OP poisoning is a medical emergency, typically requiring intensive care. Treatment involves administration of antidotes, such as atropine, respiratory and cardiovascular support, and decontamination procedures
- There is no satisfactory conventional treatment for chronic OP poisoning. Evidence has been presented that oral supplementation with coenzyme Q10 may provide symptomatic relief in chronic OP poisoning.

On a separate but nursing-relevant issue, a recent UK-based study concluded (perhaps surprisingly) that patients fatally poisoned by pesticides (including OPs) could still provide a source of organs (particularly kidneys and corneas) for successful transplantation (Mistry et al, 2018).

Conclusion

In the UK, OP poisoning is most likely to be encountered in chronic form in agricultural workers, particularly middle-aged or older sheep farmers. Although there is no satisfactory conventional treatment for chronic OP poisoning, evidence has been presented in the present article that oral supplementation with coenzyme Q10 may result in significant symptomatic improvement. Because of the increased risk of terrorist-type attacks using nerve agents in the UK, nurses may also encounter OP poisoning in acute form, the treatment of which has also been summarised in this review. **BJNN**

Declaration of interest: David Mantle is medical adviser at Pharma Nord (UK) Ltd.

CPD reflective questions

- What have you learned about organophosphate (OP) poisoning from reading this article?
- How would you apply what you have learned about OP poisoning to your nursing practice?
- How would you use your knowledge of OP poisoning to advise other categories of healthcare professionals who may be unfamiliar with this subject?

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