ISSN 1391-0736

The Sri Lanka Prescriber

September 2013; Volume 21, No. 3

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The Sri Lanka Prescriber *is sponsored by the State Pharmaceuticals Corporation of Sri Lanka as a service to the medical profession.*

The Sri Lanka Prescriber

Copies of the *Sri Lanka Prescriber* and inquiries from M. P. Kuruppu, Deputy General Manager, Marketing, and Ms Anusha Gunatilleke, Manager Promotions and Publicity (Telephone 2338102), State Pharmaceuticals Corporation, P. O. Box 1757, 75, Sir Baron Jayathilake Mawatha, Colombo 1.

Price per copy Rs 50.00 (students Rs 25.00). Personal callers may also obtain copies from the Departments of Pharmacology at the Medical Faculties in Colombo, Galle and Sri Jayewardenepura.

Published by

Department of Pharmacology
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and
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E-mail: prmanager@spc.lk Web site: www.spc.lk

Printed by

Ananda Press
82/5, Sir Ratnajothi Saravanamuttu Mawatha,
Colombo 13.
Telephone: + 94 11 2435975
E-mail: anpress@sltnet.lk

Cover picture

LOUIS HÉBERT, FIRST CANADIAN APOTHECARY (1605 A.D.)

Parisian Apothecary Louis Hébert in 1605 helped Champlain establish Canada's first settlement at Port Royal (Nova Scotia); cared for its sick, and cultivated drug plants. Later, at Quebec, he established the first farm in Canada.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Management of obstetric antiphospholipid syndrome

Introduction

In 1983, Professor Graham R.V. Hughes, described a new disease characterised by venous and arterial thrombosis, recurrent fetal loss, and thrombocytopenia in the presence of a lupus anticoagulant (LA), elevated anticardiolipin antibodies (aCL), or both [1]. Later it was shown that antibodies were directed not only to cardiolipin but also to other phospholipids, and the name was changed to 'antiphospholipid syndrome' (APS) [2]. The syndrome was originally recognized in patients with systemic lupus erythematosus (SLE). Soon it became clear that APS could occur in patients without any underlying disease, the so-called 'primary antiphospholid syndrome' (PAPS). APS is categorised as secondary if it occurs in an individual with SLE or any other collagen vascular disease. Primary and secondary APS are almost indistinguishable, clinically and antiphospholipid antibody (aPL) specificities. APS affecting pregnancy, termed obstetric antiphospholipid syndrome is now recognized as an entity distinct from vascular APS.

Antiphospholipid antibodies (aPL)

Antiphospholipid antibodies are a group of autoantibodies directed against phospholipid binding proteins that can be broadly categorised into two types; antibodies that prolong phospholipid-dependent coagulation assays, known as lupus anticoagulants (LA), or anticardiolipin antibodies (aCL),where the target is a cardiolipin (a bovine cardiac protein). Some anticardiolipin antibodies require the presence of the plasma phospholipid-binding protein, beta 2 glycoprotein-1, in order to bind to cardiolipin. This is a feature of anticardiolipin antibodies from patients with SLE or the antiphospholipid syndrome but not from patients with syphilis or other infectious diseases.

Antiphospholipid antibodies (aPL) and APS

Approximately 30 - 40% of women with SLE have aPL antibodies [3]. Some have or will develop APS. For the diagnosis of APS, in addition to aPL, a patient must have clinical features of vascular thrombosis or relevant pregnancy morbidity. Thrombotic APS is a major adverse prognostic factor in patients with lupus. In the general population, aPL antibodies are detected in 1:5 patients who have had a stroke under 50 years of age, and about one-fourth of patients with deep vein thrombosis had aPL antibodies.

Pathogenesis of pregnancy loss in APS

Recent experimental observations suggest that altered regulation of complement can cause and may perpetuate complications of pregnancy. Antiphospholipid antibodies mediate pregnancy complications by initiating activation of the complement cascade. Local increase in complement activation fragments is highly deleterious to the developing fetus.

Diagnosis of APS

Diagnostic criteria were proposed first in 1999 in Sapparo, Japan and updated in 2006, in Sydney. According to these criteria APS is present in patients with at least one clinical and one laboratory criterion (table 1).

Preconception evaluation of APS

Preconception assessment of the risks of pregnancy and treatment should be followed by appropriate counselling. Pregnancy should be discouraged in all women with significant pulmonary hypertension because of the high risk of maternal death, and should be postponed in patients with recent thrombotic events, especially stroke. A complete profile of aPL antibodies, including repeated tests for anticardiolipin and lupus anticoagulant, should be available before planning of pregnancy. APS patients already taking warfarin should be informed of potential teratogenic effects. Once pregnancy is confirmed, oral anticoagulation should be immediately stopped and switched to low-molecular weight heparin (LMWH) for the rest of the pregnancy.

Table 1. Diagnostic criteria for obstetric APS

Clinical criteria

1. Objectively confirmed arterial, venous, or small-vessel thrombosis, or
2. Pregnancy morbidity as defined by
    i. recurrent fetal loss before the 10th week of gestation, or
    ii. one or more unexplained fetal death at or beyond the 10th week of gestation, with normal fetal morphology, or
    iii. premature birth before the 34th week of gestation due to placental insufficiency, eclampsia, or preeclampsia.

Laboratory criteria

1. Medium or high titre, of IgG or IgM aCL
2. Presence of LA on 2 or more occasions at least 12 weeks apart.
3. Presence of anti-β2-glycoprotein 1, both IgG and IgM,

Presence of any one clinical and one laboratory criteria are needed for diagnosis

Obstetric complications of APS

About 10-15% of women with recurrent miscarriages are diagnosed with APS. Fetal death in the second or third trimester of pregnancy occurs in up to 5% of pregnancies. Antiphospholipid antibodies are associated with higher risk of pre-eclampsia and eclampsia compared to controls. About 25% of women having intrauterine growth restriction (IUGR) fetuses had aPL, and women with aPL deliver infants who are small for gestational age.

Fetal complications in obstetric APS

The most frequent fetal complication in APS is recurrent pregnancy loss. Most pregnancy losses occur before 10 weeks of pregnancy due to the presence of aPLs. The Euro-Phospholipid Project study, which analysed the clinical characteristics of 1000 patients with APS during a 5-year follow-up, estimated incidence of other fetal complications. Prematurity was noted in 28%, IUGR due to placental insufficiency in 11%, and stillbirth occurred in 7%.

Treatment of APS in pregnancy

The mainstay of treatment is with heparin and aspirin. Without treatment, the chance of successful pregnancy is around 30%, and it increases to 50% with low dose aspirin alone. With both aspirin and heparin, more than 70% of pregnant women with APS will deliver a viable live infant. A 2005 Cochrane systematic review concluded that women with recurrent miscarriage and APS should be given a combination of heparin 5000 IU subcutaneously twice daily and low-dose aspirin [4]. Expert guidelines recommend the combination of aspirin with either low-dose heparin or LMWH [5]. Heparin is the anticoagulant drug of choice during pregnancy. Heparin does not cross the placenta and is widely considered safe for the embryo and fetus. Both unfractionated heparin (UFH) and LMWH act primarily by binding to antithrombin. UFH enhances the activity of antithrombin for Factor Xa and thrombin, whereas the predominant effect of LMWH is via antithrombin mediated anti-Factor Xa activity.

UFH has complex pharmacokinetics that ultimately lead to a somewhat unpredictable anticoagulant response. Also, the bioavailability of the UFH after subcutaneous (SC) injection is reduced compared with intravenous infusion. LMWH, in contrast, is less likely to bind non-specifically to various circulating proteins or cell surfaces, and so has improved pharmacokinetics and bioavailability when given SC. In addition, LMWH is less likely than UFH to cause heparin-induced thrombocytopenia (HIT) and osteoporosis, though osteoporosis is infrequent (1-2% of cases) in women treated during pregnancy. Table 2 summarises recommended treatments for different groups of patients with APS.

Table 2. Treatment of different clinical situations of obstetric APS

Clinical situation	Suggested treatment
aPL positive with no history of thrombosis or pregnancy loss	Low dose aspirin (LDA) given due to low risk of toxicity
Women with APS and recurrent first trimester abortions	LDA + LMWH (benefit > 13 weeks doubtful) • Enoxaparin 20mg/day or • Dalterparin 2500IU/day
Women with APS and second or third trimester pregnancy loss, IUGR, pre-eclampsia or abruption	LDA from preconception LMWH after intrauterine pregnancy confirmed • Enoxaparin 40mg/day or • Dalterparin 5000IU/day
Women with APS and previous thrombosis	Most would be on warfarin Change to LDA + LMWH • Enoxaparin 40mg/day or • Dalterparin 5000IU/day Double the dose at 16-20 weeks
Women with APS and previous arterial thrombosis (especially stroke)	• Enoxaparin 40mg/bd or • Dalterparin 5000IU/bd If neurological features develop while on this full anticoagulation doses, may need warfarin in second trimester
Women with APS and pregnancy loss while on aspirin and LMWH	Prednisolone and hydroxychloroquine may be tried.

Other therapies – steroids in obstetric APS

About 20% patients suffer from miscarriages and adverse pregnancy events despite aspirin and heparin therapy. High dose steroids (40- 60 mg) showed no clear benefits but increased side-effects of preterm delivery because of premature rupture of membranes or preeclampsia. A recent study suggested that the addition of low-dose prednisolone (10 mg) from the time of positive pregnancy test up to 14 weeks of gestation may be effective in increasing live birth rate [6].

Hydroxychloroquine in obstetric APS

This drug is well established in treating SLE and has also been linked with a reduced risk of aPL-associated thrombosis. Effect may be mediated by a reduction in the binding of aPL and beta 2GPI complexes to lipid bilayers. Hydroxychoroquine may work in failures on aspirin and heparin. Hydroxychloquine may be particularly helpful in those with SLE and aPLs who lack manifestations of APS [7].

Intravenous immunoglobulins (IVIg) in obstetric APC

IVIg has not been shown to be superior to heparin and aspirin in unselected patients. This was confirmed in a multicentre clinical trial that tested the effect of IVIg compared with LMWH plus low-dose aspirin for the treatment of women with APS and recurrent miscarriage [8].

aPLs and unexplained sterility

Recent evidence has shown the ability of aPLs to affect implantation, placentation and early embryonic development. Hence aPLs may also be responsible for sterility. A significantly higher positivity for aPLs was found in infertile couples when compared with fertile negative controls. Studies have shown the ability of aPLs to exert a direct negative effect on uterine endothelium and pre-implantation embryos which could contribute to infertility. Although still not included into guidelines, it would be advisable for patients undergoing fertility treatment to be tested for aPL and if found positive, consider treatment with aspirin with or without heparin before in-vitro fertilization and embryo transfer. The benefits of heparin would be twofold; heparin may support the development of a favourable endometrium for implantation and reduce the risk of thrombotic complications that may occur with hormone treatment for ovarian stimulation in the presence of aPL.

Outcome of babies born to mothers with APS

The European antiphospholipid forum has recently published the results of a multicentre prospective registry including a cohort of babies born to mothers with APS in seven European obstetric centres [9]. No neonatal lupus, SLE, or thrombotic events have been recorded during the 5-year follow-up. Transplacental transfer of aPLs occurred in these pregnancies as indicated by the presence of aPL in babies. As shown in two previous retrospective reports showing learning disabilities in children born to mothers with APS, the European registry also reported that the prevalence of neurodevelopmental disabilities was twofold higher than the general population (1%). These abnormalities included hyperactive behaviour, feeding disorders, language delay, and autism. The presence of autism was recently found to be more prominent in children born prematurely and/or weighing less than 2 kg. Because of the high rate of prematurity and small for gestational age neonates in the APS group, this could be a determinant of neurodevelopmental abnormalities in APS-exposed children.

Conclusion

Obstetric APS is an entity with high pregnancy complications for both mother and fetus. Low dose aspirin and heparin improve the chances of a woman with APS having a live and healthy baby. Counselling, multidisciplinary management, and tight follow-up are the keys to successful pregnancy.

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Principles of prescribing for persistent non-cancer pain

Summary

Chronic pain (persistent and recurrent) is a major cause of distress and disability in the community.

Patients need to be comprehensively assessed to determine the biomedical, psychological, social and cultural contributions to their pain.

Although drug therapy is only part of a multimodal approach to management, its role in modifying distress is important.

Paracetamol, opioids and some antidepressants and anticonvulsants are used to treat chronic pain. A combination of these drugs is often needed for adequate pain relief.

Parenteral and short-acting oral opioids should be avoided for long-term persistent pain.

Drug treatment should be seen as a trial of therapy. Monitoring its effectiveness and safety and the patient's quality of life should guide treatment.

Key words: antidepressants, gabapentin, opioids, paracetamol, pregabalin, tramadol

(Aust Prescr 2013;36:113-5)

Introduction

Chronic non-cancer pain is a major source of distress and disability in the community. It can become a problem in its own right, even when underlying predisposing conditions are being managed optimally.

Although pain is appreciated conceptually in a 'biopsychosocial' framework that identifies somatic, psychological, societal and cultural contributions, the person in pain is still commonly managed through a narrow biomedical model, where the emphasis is on finding – and treating – an underlying pathological condition. However, this model may not work in some instances of musculoskeletal pain, as pathologies such as osteoarthrosis or spondylosis do not reliably predict distress or disability and the underlying 'disease' is essentially untreatable.

Most patients with chronic non-cancer pain are likely to experience some pain for the rest of their lives. Pain itself is the problem – not as a symptom of something else, not as a broken part to be fixed, not as a disease, but as a persistent or recurrent distressing experience.

The aims of medical management should be:

- to reduce distress to a bearable level
- to help the person function as well as possible
- to minimise the adverse effects of treatments.

Comprehensive patient assessment

The fundamental clinical approach of identifying a treatable somatic cause applies as much to persistent pain as to any other symptom. However, chronic pain is commonly due to altered central nervous system function, including central sensitisation of nociception. Recognising clinical features of altered nociception, such as allodynia, hyperalgesia and hyperpathia, and not 'chasing' structural pathology in the absence of clinical indicators is important (Box).

Identifying 'non-somatic' contributions to the pain is just as relevant. These include what is happening to the person such as mood, impact on activities of daily living, work, recreational activity, sleep and nutrition. It is also worth asking about their family, relationships and events in their life that could cause distress.

Non-drug therapies

Managing a patient's beliefs and expectations about their diagnosis and prognosis and the treatment can be difficult, but is important. The most powerful therapy is adequate explanation, emphasising the complex interaction between the somatic,

psychological and social components that contribute to the pain. Advice regarding the use of the painful part of the body, the role of exercise programs and sleep hygiene can be helpful. Support from a physical therapist, occupational therapist, psychologist, social worker or rehabilitation counsellor may be appropriate.

Box

Features of neuropathic pain

Allodynia	pain in response to normally innocuous stimulus such as touch, pressure or movement
Hyperalgesia	an increased response to a stimulus that normally evokes pain
Hyperpathia	a painful syndrome, characterised by increased reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. Faulty identification and localisation of the stimulus, delay, radiating sensation, and after-sensation may occur.

Pharmacotherapy as part of an overall strategy

Pharmacotherapy should only ever be part of a multimodal plan. Drugs are used here mainly to control symptoms and reduce distress as an adjunct to non-drug therapy. In some situations where the mechanism of pain can be confidently determined, such as inflammatory or 'neuropathic' conditions, anti-inflammatory or anti-neuropathic drugs may be helpful.

Drug treatment in chronic pain should be seen as an ongoing trial of therapy, addressing the question of effectiveness – is this patient's predicament responsive to this medication? The goals are beyond pain relief alone and should also relate to improvements in physical, emotional and interpersonal function. A treatment plan can be helpful. The following criteria can be used to monitor response:[1]

- analgesia (reduction - not elimination - of pain)
- activity (as negotiated with the patient)
- adverse effects
- affect (the patient's feelings or emotions)
  behaviours indicative of unsanctioned use (for patients prescribed opioids).[2]

Inappropriate use of opioids does not necessarily equate to addiction, but may reflect a chaotic lifestyle, psychological or physical dependence or inadequate treatment of pain. Other possibilities include a search to relieve comorbid depression or anxiety, preoccupation with being unwell or a search for sympathy, meaning or a social context. Appropriate responses include comprehensive re-assessment, a program to stabilise opioid intake (possibly including urine drug testing or restricted dispensing) and referral to a pain clinic or addiction medicine service.[2,3]

How effective are drugs for chronic pain?

Finding good evidence for drug efficacy in chronic pain is difficult because of the heterogeneity of clinical trial populations, lack of consideration of psychosocial influences on the pain experience, variable primary outcomes and generally poor quality studies.

Most literature concerns 'neuropathic' pain and is difficult to extrapolate to the clinic, as most trials have been performed in clearly defined states such as diabetic neuropathy or postherpetic neuralgia. However, the liberal definition of neuropathic pain has led to drugs being used 'off-label' in a variety of painful conditions.

In chronic pain trials, the efficacy of drugs is often expressed as the number needed to treat. Calculating this is typically based on a minimum of a 50% reduction in pain intensity, which may exclude patients with a smaller but clinically meaningful reduction. In trials over 8-16 weeks, drugs with different mechanisms (tramadol, opioids, antidepressants, gabapentin and pregabalin) have been found to be similarly effective for chronic pain. The numbers needed to treat for 50% pain reduction ranged from 2.6 to 6.4 with large 95% confidence intervals for different drugs in different conditions.[4,5]

Paracetamol

Paracetamol remains the baseline analgesic for persistent pain. It can be taken around the clock or in anticipation of activity that may worsen pain or before going to bed.[6] The extended-release form may improve adherence.

Tramadol

Tramadol has been shown to have consistent efficacy in various chronic pain states. However, adverse drug reactions with tramadol are common.[7]

Opioids

Injectable and short-acting oral opioids are not appropriate for long-term management of persistent pain. Oral controlled-release or transdermal opioids are recommended.[8]

The effectiveness and misuse of strong opioid agonists in chronic pain is the subject of current controversy.[9,10] A practical approach has recently been proposed.[2,3,11] Numbers needed to treat of 2.6 (95% confidence interval 1.7-6.0) have been quoted.[5]

Non-steroidal anti-inflammatory drugs

In most instances of chronic pain, inflammation is not the relevant mechanism. Given their potential for interaction with other drugs for common comorbidities and their adverse effect profile, non-steroidal anti-inflammatory drugs might be limited to short-term use only, for incident pain in patients who respond. They should be avoided in older patients if possible.[6]

Antidepressants

Low doses of tricylic antidepressants (amitriptyline, nortriptyline, dothiepin, imipramine) have been used for many years to treat chronic pain. The number needed to treat is 2-4,[5] but anticholinergic adverse effects are often limiting.

The serotonin and noradrenaline reuptake inhibitors duloxetine and venlafaxine have documented efficacy in painful polyneuropathy.[4] Duloxetine is reported to be effective in chronic musculoskeletal pain (fibromyalgia).[12] Selective serotonin reuptake inhibitors have been studied in a few trials and have demonstrated a weak analgesic effect.[5]

Chronic pain is often associated with changes in mood. Comorbid depression or anxiety needs to be managed appropriately, including using full doses of an antidepressant if necessary. Low-dose tricylics are not effective for treating depression.

Anticonvulsants

The use of antiepileptic drugs in true neuropathic pain (where there is neural pathology) is rational, but evidence is available only for gabapentin and pregabalin in diabetic neuropathy or postherpetic neuralgia.[5] These drugs bind the alpha-2 delta subunit of voltage-gated calcium channels of primary afferents channels, interfering with the release of neurotransmitters such as substance P, noradrenaline and glutamate. Pregabalin in relatively large doses has been effective in chronic musculoskeletal pain.[12]

Evidence for other antiepileptic drugs such as lamotrigine, topiramate and valproate in chronic pain is very limited. Carbamazepine has been used in trigeminal neuralgia.

Practical pharmacotherapy

Different classes of drugs are often used in combination. All of them act on the central nervous system and, with the exception of paracetamol, share adverse effect profiles, especially drowsiness, cognitive impairment and nausea. This is why conservative dose regimens, targeting certain drugs to times of the day when sedation is desired, and awareness of drug interactions are so important.

Although it is not possible to be prescriptive regarding any order in which these drugs should be used, regimens should be rational, safe and as simple as possible. A guiding principle is to assess their ongoing effectiveness in terms of the patient's overall quality of life.

In general, chronic pain should not be treated with short-acting drugs. For patients whose pain is opioid-responsive, sustained-release oral or transdermal preparations are preferred, starting with low doses. Titration need not be rapid but the prescriber should be alert to under-dosing, especially in a patient who is demonstrating improved function and increased activity. Improved overall well-being may in fact incur incident (not breakthrough) pain. This can be addressed by modifying activity and increasing or redistributing the background drug dose rather than adding a short-acting drug.

From comparative trials in painful polyneuropathy and postherpetic neuralgia, there is little difference in efficacy between opioids, tricyclic antidepressants, gabapentin and pregabalin.[5] Extrapolation to other clinical situations is empirical.

There is probably a limit to drug-responsiveness and it is unlikely that chronic pain can be eliminated. The aim is to establish the lowest dose of drug that is associated with overall improvement in quality of life. Any reduction in dose should be made slowly. The rule of thumb is a 10% reduction of the daily dose each week.[8]

Conclusion

Drug treatment is only ever part of a multimodal plan for the patient experiencing chronic pain. The aim is to reduce distress by controlling symptoms, as an adjunct to non-drug therapy, and thereby to improve function and quality of life. The main drugs available are paracetamol, tramadol, strong opioid agonists, tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors and alpha-2 delta binding drugs. Drug treatment is an ongoing trial of therapy and requires regular review.

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Self-assessment questions

Select the **best** response in each question

Question 1

Fibromyalgia (chronic widespread pain)

(a) prevalence is equal in men and women
(b) is commonest in the 30-50 age group
(c) is characterised by a raised ESR
(d) sufferers have a characteristic sleep disturbance
(e) pain is confined to large synovial joints

Question 2

In the pharmacological treatment of distress due to pain in fibromyalgia (chronic widespread pain) the recommended baseline and routine analgesic is

(a) tramadol
(b) a non-steroidal anti-inflammatory drug
(c) a tricyclic antidepressant
(d) an antiepileptic (eg. valproate, topiramate)
(e) paracetamol

Question 3

Diagnostic criteria for obstetric antiphospholipid syndrome include

(a) thrombocytopenia
(b) one or more premature births after 35 weeks of gestation
(c) one instance of foetal loss after 35 weeks of gestation with abnormal fetal morphology
(d) presence of lupus anticoagulant on two or more tests at least 12 weeks apart
(e) hypertension and proteinuria from early weeks of pregnancy

Answers to self-assessment questions

Question 1. The best response is **d.** Prevalence (of CWP) is much higher in women M:F = 1:7, and the commonest age group is 45-65 years. There are no helpful laboratory tests for CWP, and pain is not confined to joints.

Question 2. The best response is **e**, because of relative freedom from side-effects and sustained efficacy in most CWP patients. See second article, this issue.

Question 3. The best response is **d.** See table 1, first article, this issue.

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I have no conflicts of interest regarding the above questions and answers.

ISSN 1391-0736

Printed by Ananda Press, Colombo.