THEIR USE TO TREAT NEUROPATHIC PAIN

Antiepileptic drugs (AEDs) have been widely studied and prescribed for the relief of pain, especially neuropathic pain. Similarities between epilepsy and neuropathic pain have been observed for over 100 years (Trousseau described trigeminal neuralgia as "epileptiform" in 1885). It followed that using drugs that treat epileptic seizures might be of benefit in relieving neuropathic pain; in 1942, phenytoin was used to treat facial neuralgia(i) and in 1962(ii), carbamazepine came into use and has subsequently remained the most widely used AED to combat neuropathic pain, until the recent introduction of gabapentin, which is currently very popular with pain specialists.

Like antidepressants, anticonvulsants have NNT (Number needed to treat) of between 2 and 3 (i.e. 2 or 3 patients will need to be treated for every 1 successful outcome). This indicates that they are very effective.

FIRST AND SECOND GENERATION AEDS

First-generation AEDs include:

Sodium valproate

Carbamazepine

Second-generation AEDs include:

Gabapentin

Lamotrigine

Felbamate: NB:although this drug looked very promising, it was found that it caused serious adverse effects such as aplastic anaemia and liver failure; it is still used for certain rare clinical conditions but is NOT recommended for use to treat neuropathic pain.

Topiramate

HOW DO THEY WORK? (PHARMACODYNAMICS, or how the drug affects the body)

It is thought that they have dual modes of action:

(i) blockade of sodium channels

(ii) potentiation of GABAergic neurotransmitter system*

* the GABA system essentially "calms down" the nervous system. (is more inhibitory rather than excitatory)

* The dorsal horn neurones in the spinal cord contain cells which use GABA as their inhibitory neurotransmitter. These neurones are known to be involved in pain pathways.

Gabapentin does not appear to act at GABA receptor sites even though it was developed as a GABA analogue. Hansen (iii) suggests that allodynia may respond to gabapentin because of an effect on the GABAA receptor which inhibits large afferent (A beta) excitatory input. Other research(iv) has shown that gabapentin mimics GABAb receptor activation, but is active independently of the GABA receptor mechanism. This is borne out clinically by the effect gabapentin has on reducing muscle spasm. Shimoyama et al(v) recently concluded from their

animal studies that "The antinociceptive effects of GBP may involve the inhibition of the release of excitatory amino acids from presynaptic terminals."

* Other new AEDs associated with the GABA-ergic system inlcude tiagabine and vigabatrin.

* Although topiramate and felbamate were shown to enhance GABA-mediated events, they have additional mechanisms of action, including blockade of voltage-dependent sodium channels and inhibition of glutamatergic neurotransmission.(vi)

* Lamotrigine affects glutamate release.(vii) It is also thought to inhibit voltage-sensitive sodium channels, thereby stabilising neuronal membranes.

* Valproate slows recovery rate of voltage-gated sodium channels and limits repetitive firing. It also increases GABA levels via its effects on various enzymes.

* Carbamazepine slows recovery of sodium channels and also has a minor anatagonistic effect on calcium channels. It is chemically related to tricyclic antidepressants.

PHARMACOKINETICS (how the body affects the drug):

Carbamazepine is metabolised in the liver and can cause enzyme induction which may affect the metabolism of other drugs (see DRUG INTERACTIONS). It takes about 3-10 days to reach steady state (steady plasma level).

Valproate is metabolised in the liver and causes enzyme induction. It takes 2-4 days to reach steady state.

Gabapentin is not bound to plasma proteins, does not induce hepatic enzymes and is not metabolized. At steady state (after 1-2 days of same dose), it has a half-life of 6-8 h, and is eliminated unchanged via the kidneys

Lamotrigine is rapidly absorbed when taken orally, peak plasma levels being reached in 1.5-4 hours. Its half-life once it reaches steady state (after 5-15 days) is 33 hours. It is metabolised by the liver (it can induce its own metabolism and also that of other drugs); metabolites and unchanged drug being excreted in the urine.

Topiramate is metabolised in the liver but does not affect hepatic enzymes. It takes 4 days to reach steady state.

Second generation AEDs have a wide therapeutic window (i.e. between dose required for therapeutic effect and that which is toxic) EXCEPT felbamate.

Most second generation AEDs do not cause liver enzyme induction (which can affect the way in which other drugs are metabolised).

CLINICAL APPLICATIONS OF GABAPENTIN

Houtchens et al (viii) conducted a trial using gabapentin to treat pain due to MS in 25 patients. They reported that "Excellent to moderate pain relief was obtained in a substantial number of patients. Throbbing pains and needles, and cramping pains responded best, and dull aching pains responded least to the medication."

Also in 1997, Rosenberg et al (ix) reported on the use of gabapentin to treat neuropathic pain, chiefly post-herpetic neuralgia , sympathetically-maintained pain (in Reflex Sympathetic Dystrophy) and phantom limb pain. They concluded that "Gabapentin may be a useful adjunct for treating neuropathic pain with a minimum of side effects. Particular advantage may be gained with the use of this drug for postherpetic neuralgia and direct peripheral nerve injuries."

Mellick & Mellick (x) looked at gabapentin to treat Reflex Sympathetic Dystrophy, a condition which involves neuropathic pain and other neurogenic symptoms usually in one limb, often after trauma. In a small study of 6 patients, they found significant improvement was effected by use of gabapentin and one patient was actually cured of hyperpathia, allodynia, hyperalgesia and early skin and soft tissue manifestations, this being the first documented cure of the condition using gabapentin alone.

However, in 1997, Wetzel and Connolly (xi) pointed out that up until then, the majority of

published studies involved small series of patients and limited data and therefore recommended that further larger studies using established protocols be undertaken. They further suggested that "Gabapentin should only be considered for pain management after well-established therapies have failed to produce desired outcomes."

In 1998, Merren (xii) conducted a large case series looking at gabapentin for treatment of pain and tremor. He looked at the results of treating 59 patients who had diagnoses such as central neurogenic pain, peripheral neuropathy, arachnoiditis, trigeminal neuralgia, post-herpetic neuralgia and restless legs syndrome as well as essential tremor and benign familial tremor. 68% of the patients reported improvement, of which 65% had moderate-to-excellent response. The best response was found in patients with peripheral neuropathy and trigeminal neuralgia. Of 3 arachnoiditis patients treated, one discontinued due to adverse effects and the other 2 had moderate improvement in pain level. Treatment of benign essential/familial tremor was successful in 7 patients (6 moderate, 1 excellent control).

Also in 1998, there were 2 large studies published in the Journal of the American Medical Association.

One study (xiii) looked at the effects of gabapentin in treating the pain caused by diabetic neuropathy (DPN). It showed that there was a significant reduction in pain after treatment and that 26% of patients treated with gabapentin (neurontin) were pain-free at the end of the trial compared with 15% treated with placebo (which is a statistically significant difference). One of the authors, Dr. Edwards (director of the Neurological Research Centre, Bennington) said in interview "DPN is a neuropathic condition that is, historically, extremely difficult to treat...this study is one of the largest of its kind in this condition. In patients with DPN, gabapentin substantially reduced neuropathic pain and was well tolerated."

"Further, more significant pain reduction was observed in some patients after only two weeks of treatment."(xiv) The study also found that gabapentin reduced interference of sleep by pain and had some positive effects on mood and quality of life.

The second study looked at post-herpetic neuralgia (PHN) and again was a randomised double-blind study. (xv) Almost twice as many patients treated with gabapentin were pain-free compared with those treated with placebo (16% versus 8.8% respectively). Many patients experienced a significant reduction in pain after treatment with gabapentin.

(Note: Diabetic peripheral neuropathy: Diabetes is a condition in which the body either fails to produce or respond to insulin, a hormone which is vital in regulating blood sugar. Nerve damage may occur, commonly in the lower extremity, especially the feet and ankles.

Post-herpetic neuralgia: severe nerve pain following an attack of shingles (herpes zoster). Some 15% of PHN sufferers have persistent pain after the rash has resolved and this pain may persist for months or even years.)

Solaro et al (xvi) found that gabapentin is effective in treating hypertonia (increased muscle tone), painful tonic spasms and paroxysmal paresthetic disturbances (PPD) seen in Multiple Sclerosis. Some of these symptoms are seen in other conditions such as arachnoiditis.

A recent study (xvii) has confirmed that gabapentin reduces the impairment of spasticity in Multiple Sclerosis.

Serrao et al (xviii) have found that gabapentin is helpful in treating muscle cramps; their open label trial results were published earlier this year and they suggested that a dose of 600-1200mg/day may be effective in controlling muscle cramps, which can be experienced in a number of different conditions.

OTHER AEDs

Sodium valproate (Divalproex)

Authors such as Loscher (xix) have reported the use of valproate in treating neuropathic pain. I am also aware of its use in centres in Australia, at a dose of 200mg three times a day increasing to 500mg three times a day, apparently with a good degree of success. However, Wiffen et al, in the Cochrane Report on "Anticonvulsant drugs for acute and chronic pain"(xx), stated "The only placebo-controlled study in acute pain found no analgesic effect of sodium valproate."

Lamotrigine: (Lamictal)

Lamotrigine is a second generation AED. In 1996, Canavero et al (xxi) reported beneficial effects of lamotrigine in 4 patients who suffered from central neuropathic pain. In 1997, Harbison et al (xxii) reported success in treating 3 patients with phantom limb pain and stump hypersensitivity, Post-herpetic neuralgia (PHN) and causalgia respectively. In 1998, at the Eighth Annual Neuroscience of HIV Infection meeting in Chicago, the results of a small study of patients treated for HIV related peripheral neuropathy with lamotrigine were presented. Although this was a small study, there was a significant difference between the test group and the control group who received placebo. Some patients reported pain relief within 2 weeks of starting treatment with lamotrigine. (xxiii) This randomised, controlled trial was sufficiently encouraging to warrant further studies. In 1998, di Vadi and Hamann(xxiv) published an article on the use of lamotrigine in treating neuropathic pain in just 2 patients and again suggested that "this novel channel antagonist can be used to treat neuropathic pain. Double blind placebo control studies are therefore needed to substantiate these findings."

In October 1999, McCleane (xxv) published the results of a randomised, double-blind, placebo controlled trial involving 74 patients. He did not find any therapeutic effect at doses up to 200mg/day for an 8 week period of treatment.

Topiramate (Topamax)

In 1998, at the American Academy of Neurology 50th Annual Meeting, Dr. Keith Edwards, a Neurology Consultant from Vermont, presented a small study of 14 patients who were treated for refractory neuropathic pain with topiramate. After being treated for 3 months, the patients reported significant reduction in pain. Th average dose of topiramate was 270 mg/day (range 100-800mg/day). The dose was increased or decreased in 25-50mg increments as necessary and the first report of pain relief came at a dose of 214mg/day. As Dr. Edwards stated, these results suggest that further randomised controlled trials should be undertaken to confirm these results. (xxvi)

Zonisamide(Zonegran)

This sulfonamide anticonvulsant was approved by the FDA in March 2000. It is used in various epileptic conditions, but is also currently being studied at the University of Wisconsin to determine its possible application in treating neuropathic pain.

DOSES:

Carbamazepine: (Tegretol)

It should be started slowly, provided that the patient's pain is not out of control. A starting dose of 100-200mg at bedtime is recommended. The patient should be warned about side-effects such as dizziness, sedation, confusion and rash. The dose should then be carefully titrated upwards in 100-200mg increments in equally divided doses every 2-3 days, side-effects permitting, until pain relief is obtained or the maximum daily dose of 1,200mg is reached. On average, the usual dose is 200mg 8hourly, although occasionally 400-600mg 8 hourly may be reached.

Aplastic anaemia is a rare side-effect of carbamazepine and this small risk necessitates baseline blood test and a rigid monitoring programme for the first few months.

Routine monitoring of drug levels in the blood is not necessary, although it may be helpful to obtain this data in the event that side-effects are troublesome at sub-therapeutic doses.

It is important to maintain a therapeutic level for several months and the drug should not be discontinued abruptly.

Gabapentin : (Neurontin)

Generally, the dose should only be titrated up slowly to minimise adverse effects and to establish the minimum effective dose.

A starting dose of 300mg at bedtime for 2 nights should be followed by 300mg twice a day for 2 days, then 300mg three times a day for 2 days, and possibly if pain relief has yet to be obtained: up to 4 times a day. If partial pain relief has been gained, then further incremental increases of 100mg may be utilised up to a maximum of 3600mg per day. Waldman (xxii) suggests that relief from neuropathic pain is commonly achieved at around 900-1200mg per day. Lipman, on the other hand, refers to an effective range of 900-1800 mg a day, when used in conjunction with a TCA. He suggests that around three-quarters of patients with peripheral neuropathic pain will experience some pain relief from the combination of these medications. (xxvii) Dr. Dawn Marcus, writing in The American Family Physician (xxviii) recommends that if no benefit has been obtained by 1800mg per day, then higher doses are unlikely to be helpful, whereas partial relief at that dose suggests that higher doses may be successful in improving pain relief.

Merren (xxxvii) however, found that some patients experience troublesome sedation and he tried initiating patients with 100mg at night for 2 nights, then 100mg twice a day for 2 days; 200mg three times a day for 2 days then 300mg three times a day. His maximum dose was 2700mg.

Hansen (xxviii)recommends an 8-week trial at doses of 1800 to 2400 mg daily before treatment is considered to have failed. In his experience, pain relief is achieved within a few weeks of initiating therapy.

NB. This medication should not be discontinued abruptly.

Phenytoin: (Dilantin)

In a few patients who are unable to tolerate gabapentin or carbamazepine, phenytoin may be of help. As with carbamazepine, baseline blood data should be obtained. A starting dose of 100mg at bedtime is usual (for 2 nights), increasing by increments of 100mg, given in equally divided doses, to a maximum of 300mg daily. At this point, further blood values must be measured and then the dose can continue to be titrated up with care: preferably using paediatric doses as the kinetics are non-linear (i.e. the increase in blood level is not directly proportional to the increase in dose). It is rare for more than 400mg to be needed.

Lamotrigine:

A starting dose of 25 mg, one daily for 7 days, then 2 daily for 7 days increasing to 4 daily for 7 days, then 6 daily for 7 days and finally to take 8 daily, if side-effects allow. (i.e. 200mg/day in total). In McCleane's study (xlix) although there was little analgesia at 200mg per day, a further gradual increase may yield results; in the study, some patients gained relief at doses up to 600mg/day. However, it is vital to ensure a gradual dose increase to avoid the risk of serious rash.

It is important to note that although McCleane's study does not appear encouraging as to the efficacy of lamotrigine, there were comments from other clinicians such as Devulder (xxix) who expressed the opinion that the trial (only 56 days long) was perhaps not long enough to allow the full effects of the lamotrigine on some of the complex cellular mechanisms involved in neuropathic pain. McCleane himself responded (xxx) to Devulder's comments thus: "I would contend, despite my own results in this study, that lamotrigine is analgesic when appropriately used, and it remains my first choice anticonvulsant when treating neuropathic pain. Our failure to demonstrate this effect is, I think, a failure of study design rather than an indication of lack of effect."

ADVERSE EFFECTS:

In 1993, Morris (xxxi) described the efficacy and tolerability of gabapentin. He looked at 100 patients who were treated for epilepsy and found that at an average daily dose of just over 2000mg, "Mild adverse events, commonly somnolence, fatigue, ataxia and dizziness, have been reported in about 75% of gabapentin recipients." In 1994, Ramsay (xxxii) suggested that "Gabapentin is well tolerated.

Although adverse events occur in most patients receiving gabapentin as adjunctive therapy, they are transient and mild to moderate in severity."

Weight gain: DeToledo et al (xxxiii) looked at the effect of gabapentin on weight and found that of 44 patients studied, weight gain occurred in 10 patients who gained more than 10% of their baseline weight, and 15 patients who gained 5% to 10% of baseline.

Myoclonus: Asconape et al (xxxiv) reported recently that gabapentin may be associated with myoclonus (muscle jerks). However, the authors have suggested that it is usually mild and it is not necessary to discontinue treatment with gabapentin in most cases.

Short-term memory problems may occur with gabapentin.

Lamotrigine may cause severe rash unless it is started at a very low dose and only very slowly titrated up. However, it has been reported as well tolerated and safe.(xxxv) Potentially severe and life-threatening CDRs (including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) are estimated to occur in 1 in 1000 adults and 1 in 50 to 100 children. (xxxvi) Fatalities have occurred during lamotrigine therapy, although the exact role of lamotrigine in these cases has not been definitely established.(xxxvii) Lamotrigine has also been reported to cause anticonvulsant hypersensitivity syndrome.(xxxviii)

Vitamin D: anticonvulsant drugs can inactivate vitamin D, and thus result in bone loss (xxxix). However, this does not appear to affect people exposed to plenty of sunshine (xl). Vitamin D status can be measured by doctors.

Summary of adverse effects:

Carbamazepine: nausea/vomiting; diarrhoea; rash, pruritus (itching); fluid retention (low sodium); drowsiness, dizziness, blurred vision, lethargy, headache, tinnitus, paraesthesia (tingling), abnormal involuntary movements, leg cramps. Urinary frequency or occasionally acute urinary retention may occur.

Valproate: weight gain, nausea, vomiting, hair loss, bruising, tremor.

Gabapentin: indigestion, loss of appetite, constipation, dry mouth, sore gums, itching, fatigue, impotence, fluid retention and weight gain; pain/ burning/ tingling in hands and feet; sedation(or: restlessness), ataxia (staggering, drunken gait) dizziness.

Lamotrigine: severe rash (see above) gastrointestinal upset; dizziness, tremor, ataxia, diplopia (double vision), headache.

Topiramate: fatigue, renal calculi (kidney stones); tremor, headache, epistaxis(nosebleeds); swelling of face/lips or tongue; rash/itching; tingling/pain/numbness in hands or feet; hearing impairment; ataxia, dizziness, cognitive (thinking) difficulties; agitation/irritability; mood changes, including depression.

Carbamazepine, valproate and lamotrigine can cause rare idiosyncratic reactions such as Stevens-Johnson syndrome (all 3 can cause this), and carbamazepine and valporate can also cause(rarely) aplastic anaemia, agranulocytosis, serum sickness (all are blood disorders) pancreatitis, hepatic (liver) failure.

CUTANEOUS (SKIN) ADVERSE REACTIONS TO AEDs

Cutaneous drug reactions (CDRs) to anticonvulsants are relatively uncommon. These reactions are idiosyncratic and there are several problems in classifying and reporting CDRs. It is therefore make it difficult to determine their true incidence and causality:

Exanthematous (morbilliform) reactions are the most common.

Most CDRs are mild, but severe and life-threatening reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and anticonvulsant hypersensitivity syndrome can also occur. Management of anticonvulsant-related CDRs generally includes withdrawal of the causative drug and symptomatic therapy as required. (xli)

CDRs to gabapentin, topiramate and tiagabine have not been reported in medical literature to date.

Below is a Table depicting the various types of reaction that may occur, mild reactions at the top, more severe towards the bottom of the table.

TABLE OF CUTANEOUS DRUG REACTIONS DUE TOANTICONVULSANTS USED FOR NEUROPATHIC PAIN.

REACTION

APPEARANCE

CAUSATIVE DRUGS

Exanthema

Maculopapular(flat/slightly raised in pimples), scarlatiniform/rubelliform(red) pruritic(itchy) lesions

Benzodiazepines (BZDs) Carbamazepine, Valproate, Lamotrigine

Urticaria

Erythematous(red), pruritic(itchy) wheals. May progress to angio-oedema and anaphylaxis

Benzodiazepines (BZDs) Carbamazepine, Valproate

Fixed drug eruptions

Reddened round lesions which blister and crust. Hyperpigmentation may be permanent.

Lesions tend to present in same location if rechallenge

performed

BZDs and carbamazepine

Bullous reactions

Blisters and vesicles; may be part of more generalised CDR such as vasculitis or EM complex*

Carbamazepine

Lichenoid reactions

Flat violaceous papules resembling lichen planus

Carbamazepine

Alopecia

Hair loss,Thinning hair

Carbamazepine, vigabatrin, valproate, BZDs

Pigmentation changes

Colour changes may affect skin, hair, nails, mucous membranes; may be permanent

BZDs, Valproate

Photosensitivity

Abnormal sensitivity to UVA or UVB (photoallergy); may result in severe sunburn

Carbamazepine ; BZDs

Exfoliative dermatitis

Generalised redness, pruritus and eczema with exfoliation(skin peeling off); may affect whole body; also: fever, chills, lymphadenopathy, malaise

Carbamazepine, diazepam , valproate

Vasculitis

Small haemorrhagic macules coalescing to larger blisters and ulcers; fever, malaise, joint/muscle pain

BZDs, Carbamazepine, Valproate

Anticonvulsant hypersensitivity syndrome

Multiorgan syndrome affecting skin (exanthematous pustulation), fever, lymphadenopathy, leucocytosis(raised white cell count), hepatitis, nephritis(kidney inflammation), thrombocytopenia(low platelets), myopathy, anorexia, anaemia, pulmonary infiltrates(lung)

Carbamazepine, lamotrigine

Erythema multiforme (EM) complex*

Sudden onset skin eruption(morbilliform) with stomatitis, vesicles around lips and oral mucosa, fever, muscle pains, ocular involvement (SJS) and exfoliation 1-15% in SJS or >15% TEN of skin area

Carbamazepine, valproate

Erythema nodosum

Painful erythematous subcutaneous nodules; fever, malaise; general symptoms may persist for years.

Carbamazepine

SJS= Stevens- Johnson Syndrome; TEN= Toxic Epidermal Necrolysis

DRUG INTERACTIONS:

Carbamazepine:

* Calcium channel blockers e.g nifedipine; verapamil (may be used to treat high blood pressure); these drugs enhance the effect of carbamazepine.

* Digitoxin (for abnormal heart rhythm): reduced effect as metabolism accelerated.

* Corticosteroids reduced effect

* Diuretics ("water tablets" for fluid retention) :increased risk of hyponatraemia (low sodium)

* Danazol (hormone) enhances the effect of carbamazepine.

* Oral contraceptives: reduced contraceptive effect

* Lithium neurotoxicity may occur without raised plasma levels.

* Muscle relaxants effect may be reduced or shortened.

* Theophylline (used to treat asthma) reduced effect

* Thyroxine reduced effect

* Cimetidine (ulcer-healing) raised carbamazepine levels

* Fluoxetine (Prozac) causes raised carbamazepine levels

* Erythromycin (antibiotic) causes raised carbamazepine levels

Valproate:

* Aspirin enhances effect of valproate

* Anticoagulants (warfarin, nicoumalone) anticoagulant effect may be increased

* Antidepressants lower convulsive threshold

* Other AEDs may cause enhanced toxicity

* Antipsychotics convulsive threshold lowered

* Cimetidine increases valproate blood level

Gabapentin:

* One of the main advantages of gabapentin is the lack of drug interactions.

Lamotrigine:

* Other AEDs enhanced effects, increased sedation, may enhance toxicity

Topiramate:

* Other AEDs

* Oral contraceptives reduced contraceptive effect

* Central nervous system depressants: analgesics; muscle relaxants, hypnotics (sleeping tablets)

NB. ALL AEDs INTERACT WITH ALCOHOL.

NOTE: Clonazepam is used as an AED but is from the class of drugs called benzodiazepines, which will be in another article.

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Patron of ASG

July 2000

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