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The relevance of monitoring lamotrigine serum concentrations in chronic pain patients

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Abstract

Lamotrigine is a novel anticonvulsant initially used in epilepsy treatment. Because of its physiological properties it has subsequently been introduced in pain management and has become an interesting co-analgesic, because it inhibits release of excitatory neurotransmitters, influences different sodium, calcium en potassium channels and elevates the GABA levels.

A linear relationship appears to exist between serum concentrations, drug activity and clinical outcome. However, measurement of lamotrigine serum concentrations is very useful for daily dose adjustments in order to prevent toxic reactions. In most studies describing the neuropathic pain-relieving effects of lamotrigine, a daily oral dose of 300 to 400 mg was administered. Some of our patients received 800 mg lamotrigine with better results than when 400 mg doses were used. The serum concentrations in these patients were higher but still below the so-called dangerous level of approximately 15 mg/L. Lamotrigine itself is metabolized by conjugation to form inactive metabolites. Lamotrigine serum concentrations can be influenced by the intake of other drugs metabolized by the cytrochrome P450.

As good pain relief depends on adequate lamotrigine serum concentrations and dangerous side effects should be avoided, we recommend to monitor individual concentration levels in relation to lamotrigine dosage. However, skin rash is an important adverse effect of lamotrigine and is independent from plasma concentration levels.

Key words : Lamotrigine ; plasma serum concentrations ; pain relief ; complications ; anticonvulsants.

Introduction

Lamotrigine (Lamictal®) is an anticonvulsant, stabilizing neural membranes by blocking the activation of voltage-sensitive sodium channels and inhibiting the presynaptic release of glutamate, an excitatory neurotransmitter (Neels *et al.* 2004). Furthermore, the drug has effects on the modulation of calcium and potassium currents (Grünze *et al.* 1998). The present paper provides an overview of the pharmacological properties of lamotrigine and the clinical evidence related to its efficacy and safety, and discusses the importance of measuring serum concentrations in pain patients.

The pharmacotherapeutical arsenal for chronic pain mainly consists of paracetamol and non steroidal antiiflammatory drugs as analgesics, and of antidepressants and anticonvulsants. Anticonvulsants can be the main treatment in acute and chronic conditions for neuropathic pain. Even if analgetics and anti-inflammatory agents are the most prescribed drugs in neuropathic pain, they are the less effective because they do not act on the causes and pain mechanisms. In these conditions, anticonvulsants are the drugs of choice with antidepressants and opioids. We used lamotrigine as monotherapy in seven patients in whom other drug combinations had failed. When higher dosages were needed to obtain sufficient pain relief, we monitored the serum concentrations. Because serum levels can be influenced by different mechanisms drug efficacy can vary considerably. Combining different anticonvulsants for epilepsy has received ample consideration in the literature, but data on serum concentrations and doses of lamotrigine in pain patients are lacking. The present study was therefore designed to establish the relevance of monitoring these serum concentrations in chronic pain patients.

Methods and materials

We studied seven patients ; 3 male and 4 female caucasians with a mean age of 54 years (Table 1).

Oral daily doses of lamotrigine higher than those recommended (300 and 400 mg daily) were used in 3 patients. Three other patients received the standard dose of 300-400 mg and 1 patient obtained adequate pain relief with a much lower dose of 75 mg daily (Table 1). We monitored the patients to ascertain that toxic levels would not be reached. We also determined the serum concentration range at which adequate pain relief was obtained. All patients had neuropathic pain but some patients with failed back surgery syndrome presented

Table 1

Patient population and their characteristics : pathology and daily dose versus serum concentration and pain relief

Patient	Pathology	Daily dose lamotrigine	Serum concentration	Pain relief
Male Caucasian 53 years old	Failed back surgery syndrome	800 mg	10,3 mg/L	40-50%
Female Caucausian 69 years old	Failed back surgery Syndrome	800 mg	8,3mg/L	40-50%
Female caucasian 45 years old	Failed back surgery syndrome	800 mg	11,2 mg/L	40%
Male caucasion 64 years old	Facial pain	400 mg	6,6 mg/L	80%
Female Caucasian 40 years old.	Postherpetic neuralgia (facial pain)	75 mg	1,67 mg/L	90%
Male caucasian 43 years old	Facial pain	400 mg	7,07 mg/L	50%
Female caucasian 45 years old	Facial pain	300 mg	4,7 mg/L	50%

mixed neuropathic nociceptive pain. Concomitant medication such as opioids, or other anticonvulsants were stopped because of inefficacy. Lamotrigine titration was increased very slowly to prevent skin rash, which is a very dangerous side effect and rather common especially if titration is too rapid.

After 6 weeks of treatment dose titration was adjusted more rapidly until sufficient pain relief was achieved. Blood samples were taken after 4 weeks of stable daily dose intake (twice daily with an interval of 12 hours) and six hours after drug intake. Serum concentrations were determined by the High Performance Liquid Chromatography technique (HLPC).

Results

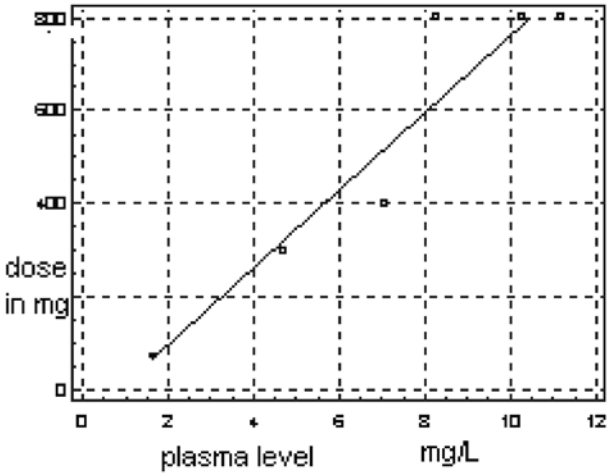
In the seven patients clinical plasma serum levels were determined. Plasma levels were lowest in patients taking the lowest dose and highest in those on an oral intake of 800mg/day. Statistical analysis (Medcalc, Microsoft for windows) revealed a significant correlation between oral intake and serum concentrations (correlation coefficient r = 0.9475 and p = 0.0041) (Table 1 and 2)

Discussion

Although in the past three decades many clinical trials assessing the efficacy of anticonvulsants for reducing pain were reported analgesia appeared to be effective in less than 50% of the patients (Sindrup and Jensen, 1999). Such outcomes may be partially attributable to the wide variability in the type of pain syndromes and to the lack of a clear understanding of the underlying neural mechanisms. Another problem is the importance of adequate dosage and the possible individual genetic polymorphisms into the cytochrome P450 enzyme, influencing drug metabolism (Wilkinson, 2005). An additional reason for the relatively high anticonvulsant treatment failure rate is the toxicity associated with their use, especially in elderly patients. Therefore, a better understanding of the relationships between mechanisms, symptoms and treatments seems to be crucial to a better selection of the proper drug for the proper patient. Moreover, a thorough appreciation of the adverse effects of the different drugs is essential to the development of strategies for minimizing these effects (i.e., slow titration or combining lower dosages of different drugs). Acute lamotrigine poisoning may result in severe encephalopathy (Sbei and Campellone,

Table 2

Correlation between oral lamotrigine dose and plasma concentrations



2001). The decribed middle- aged female patient was treated for epilepsy with the combination of lamotrigine and valproate, a drug capable of increasing lamotrigine serum concentrations. On admission lamotrigine serum concentration was 32 mg/L and valproate concentration 65 mg/L (reference 50-100 mg/L). Consequently, stupor developed. When the serum levels returned to normal, the patient made a complete recovery.

Lamotrigine has been widely used by neurologists in the treatment of epilepsy and by psychiatrists in the treatment of mood disturbances. Most of them notice that lamotrigine related side-effects are not only related to the "absolute" plasma level but also to the speed to get it (Ketter *et al.*, 2005). Adverse events of duotherapy carbamazepine and lamotrigine are mostly secondary to the increase of the carbamazepine epoxide provoked by lamotrigine (Bialer M, 2005). If valproate is added to lamotrigine, a fast increase of lamotrigine concentration can give adverse events, even if the "absolute" value is still within usual range (Hirsch, 2004). Of the newer antiepileptic drugs, lamotrigine is most frequently associated with skin rash. According to earlier reports, skin rash may occur in up to 7%-10% of patients (Wadelius *et al.* 1996, Schaub *et al.* 1994). This side effect is possibly the most import adverse effect of lamotrigine All available data indicate that lamotrigine should be discontinued at the first appearance of any rash because it cannot be predicted which rash will prove to be dangerous or life-threatening. Other common side effects include nausea/vomiting, sedation/drowsiness, dizziness, headaches, malaise, visual disturbance, and ataxia (Choi and Morrell, 2003). The overall adverse effects profile for lamotrigine is similar in males and females and is dose-related. Two double-blind placebo-controlled studies (495 patients) showed good efficacy of lamotrigine (200-400 mg/daily) in painful diabetic neuropathy. Unfortunately the drop out rate was substantial (18%) because the patients did not tolerate side effects. The majority (58%) of patients reported their overall change from baseline as "very much " or "much improved" (Tuchman *et al.*, 2005).

Given the wide variability in lamotrigine kinetics caused by interaction with concomitant medications, monitoring serum lamotrigine concentrations may theoretically be useful in clinical practice (Perruca, 1993). However, this is not routinely done in patients using lamotrigine for pain control. The use of concomitant enzyme inducers can decrease the half-life of lamotrigine by half (Patsalos *et al.*, 2002).

Lamotrigine is absorbed rapidly and completely from the gastrointestinal tract, with no effects of food on drug absorption. Oral lamotrigine availability has been established at 98% (Peck, 1991). The time to peak drug concentration varies from 1.4 to 4.8 hours. A second peak has been reported at 4 to 6 hours, possibly due to enterohepatic recirculation. Data from early trial phase 3 studies for epilepsy reported therapeutic anticonvulsant serum concentrations from 1 to 4 mg/L (Peck, 1991), while nowadays the therapeutic range is more in the range of 3-14 mg/L (Neels *et al.*, 2004).

Lamotrigine is approximately 55-56% bound to plasma proteins. Lamotrigine is a lipophylic drug that penetrates the blood-brain barrier and is therefore readily detected in brain tissue. The drug is extensively metabolized by conjugation with glucuronic acid. The known inactive metabolites are the 2-N and 5-N glucuronide conjugate and the 2-N methyl metabolite. The total body clearance of lamotrigine ranges between 0.2 to 1.2 ml/min/kg in adults and 0.3 to 3.6 ml/min/kg in children. Excretion of the drug is 94% renal, although this mode of excretion is reduced in patients with renal failure (Schaub *et al.*, 1994). Lamotrigine elimination half-life is 13-30 hours (Perruca, 1993 ; Garnett, 1996). The pharmacokinetic profile appears to be linear, and kinetic parameters after multiple dosing are similar to those observed after a single dose. This was confirmed by our observations in a small population (Table 2). Nevertheless, not all authors agree with that statement. May *et al.* reported no clear- cut relationship between clinical response and toxicity and serum lamotrigine concentrations (May *et al.*, 1996). However, the incidence of toxicity has been shown to increase with concentrations higher than 15 mg/L (Johannessen *et al.*, 2003 ; Hirsch *et al.*, 2004 ; Bialer, 2005).

Pain occurs in all age groups but older patients are more prone to have pain. Moreover, they are polymedicated and interference with metabolisation can occur. With lamotrigine in monotherapy we obtained very good pain relief with serum concentrations remaining within the safe range. It might be important that serum concentrations do not exceed 15 mg/L(Johannessen *et al.*, 2003), which is consistent with the serum concentration postulated by May *et al.*, 1996.

Based on these observations, lamotrigine can be considered a potent co-analgesic through its different modes of action and can provide good pain relief. However, some caution should be observed. In view of its longer half life therapeutic drug monitoring is advisable. Although our results show a good correlation between dose intake and serum concentrations, the maximum dose at which we can titrate patients without monitoring, connot be established. The patient who became stuporous, had a serum concentration of 30 mg/L (Sbei *et al.*, 2001) which is almost double of what is advised in Johannessen's report. In conclusion, there is increasing evidence that lamotrigine serum concentrations should be monitored in pain patients. As they are frequently polymedicated and many metabolic reactions can occur (i.e. cytochrome P450 and co-enzymes), it might be important not to

titrate higher than 15 mg/L. It is important to keep in mind that skin rash is the most important side effect and dose concentration independent.

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