Mirtazapine in Veterinary Medicine a Pharmacological Rationale for its Application in Chronic Pain

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Abstract: Problem statement: Many recent studies have shown that antidepressant agents have analgesic effects in addition to their intended primary actions. The Tricyclic Antidepressants (TCAs) have been recognized as an effective first-line treatment of human neuropathic pain but unfortunately they display a wide range of side effects. Recent studies have shown that Selective Serotonin Reuptake Inhibitors (SSRI) also have potential analgesic effects, albeit of a lower potency compared with the TCAs. Despite this, there is a trend for their increased use, in place of TCAs, in the treatment of chronic pain. Mirtazapine, a SSRI has been recently investigated in the context of veterinary medicine. It has shown favourable pharmacokinetic profiles. Despite the fact that it has mainly been used for anorexia and as an antiemetic for veterinary patients thus far, it could be potentially useful for the treatment of a wide range of anxiety-related conditions and as an analgesic in chronic and cancer-associated pain, due to its effects on both the noradrenergic and serotonic system. Rationale for the use of mirtazapine in veterinary medicine is reviewed in light of previously published literature. **Conclusion/Recommendations:** Mirtazapine is proposed as a potential analgesic for use in a multidrug analgesic regime in the context of veterinary medicine. Further studies need to be performed before it is implemented in clinical practice however.

Key words: Mirtazapine, SSRI, pain, serotonin, animals

INTRODUCTION

Many recent studies have shown that antidepressant agents have analgesic effects in addition to their intended primary actions (Lynch, 2001; Sindrup and Jensen, 1999; Davies, 1997; Spiegel *et al.*, 1983). The same studies have also demonstrated that some antidepressants may have analgesic effects. These have been found to be totally independent of their antidepressive effects and to occur at lower doses than are required for anti-depressant actions (Milligan, 1997; Bowsher, 1991; Sindrup *et al.*, 2005; San and Arranz, 2006).

The potential analgesic effects of antidepressants, particularly first-generation antidepressants such as Tricyclic Antidepressants (TCAs), have been demonstrated in many trials. Based on this research, they have been suggested for symptomatic treatment of several conditions such as neuropathic pain (Kalso *et al.*, 1996; Weber, 2001; Sindrup *et al.*, 2005), fibromyalgia (Krell *et al.*, 2005; Arnold *et al.*, 2000),

headaches and for migraine prophylaxis (Tomkins *et al.*, 2001). Such is their effectiveness; the TCAs have been recognized as desirable first-line treatment for human neuropathic pain.

Unfortunately, TCAs display a wide scale of side effects. These include drowsiness, dry mouth, blurred vision, constipation, urinary retention, vertigo, impaired sexual function, increase in heart rate, confusion or disorientation, migraine, low blood pressure, light sensitivity, increased appetite, weight gain, nausea and weakness (McCleane, 2008). Discontinuation may result in withdrawal-like side effects such as headache, nausea, vertigo, tiredness and flu-like symptoms (McCleane, 2008). TCAs have the ability to induce extrapyramidal symptoms such as acute or tardive dyskinesia, akathisia, myoclonus, rabbit syndrome and dystonia (Vandel *et al.*, 1997). The symptoms are dose, rather than age related so they can occur in anyone. They are purposeless, repetitive, involuntary and painful movements such as jerking, blinking, tongue movements and muscle spasms.

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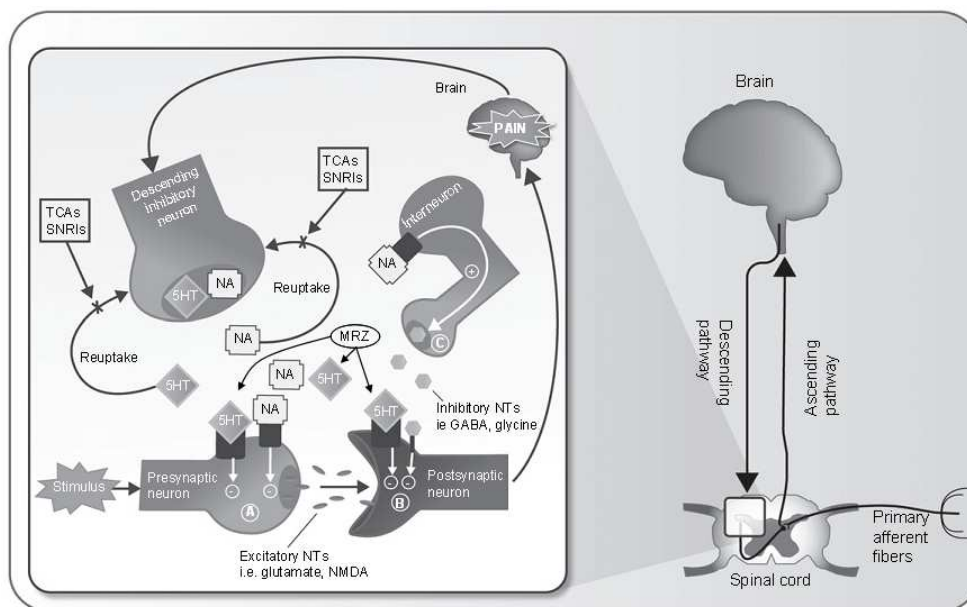Via Livornese (lato monte) 1, San Piero a Grado 56010 Pisa, Italy Tel: +39 50 2210154 Fax: +39 50 2210182

Fig. 1: Monoamine re-uptake inhibitors such as Tricyclic Antidepressants (TCAs) and Serotonin and Norepinephrine Re-uptake Inhibitors (SNRIs) are believed to promote analgesia by increasing the synaptic concentration of Norepinephrine (NE) and/or serotonin (5-HT) within the dorsal horn, thereby (A) inhibiting the release of excitatory neurotransmitter by pre-synaptic neurons; (B) reducing the excitation of post-synaptic neurons and (C) promoting the release of other inhibitory neurotransmitters by interneurons. MRT does not inhibit the reuptake of serotonin or noradrenaline, (Pinder, 1997a). Its activation of 5-HT_{1A} receptors inhibits the excitability of spinothalamic projecting neurons and excitatory interneurons, as well as promotes the $5\text{-HT}_{1B/D}$ receptor activation through inhibition of neurotransmitter release from primary nociceptive afferents (triggering an antinociceptive effect). The blockade of the 5-HT_2 and 5-HT_3 receptors reduces the likelihood of some serotonergic adverse effects associated with the nonselective serotonin receptor activation of other SSRIs

These symptoms may reoccur even with an appropriate withdrawal regime from TCAs and will not subside without medical treatment (Vandel *et al*., 1997).

TCAs can also interact with many different drugs that may be being used concurrently resulting in a considerable number of potential side effects. Interactions occur with a wide variety of drugs including alcohol, antihistamines, antihypertensive medications, antipsychotics, aspirin, bicarbonate of soda, diuretics, oral contraceptives, certain blood coagulants, sleeping medications, thyroid medications, tobacco and even some vitamins (Gillman, 2007).

Serotonin and Norepinephrine Re-uptake Inhibitors (SNRIs; e.g., duloxetine and milnacipran) have also been shown to be effective suppressors of pain (Dworkin *et al*., 2007; Attal *et al*., 2010). These agents are believed to exert their analgesic effects primarily by increasing the activity of descending pain-suppressing pathways (Fig. 1).

Several studies have shown that Selective Serotonin Reuptake Inhibitors (SSRIs) also have potential analgesic effects, but this effect is lower than that of the TCAs (Giannopoulos *et al*., 2007; Varia *et al*., 2000). Because they are associated with fewer side effects however, they have recently started to replace TCAs in the treatment of chronic pain (Miller and Rabe-Jablonska, 2005).

Mirtazapine (MRZ), belongs to the SSRI class. The antidepressant activity of this drug is thought to result from a combination of noradrenergic and serotonergic effects (Boer *et al*., 1995). MRZ enhances noradrenergic and 5-HT_{1A}-mediated serotonergic neurotransmission via antagonism of central α_2-adrenergic autoreceptors and heteroreceptors and through the postsynaptic blockade of 5-HT_2 and 5-HT_3 receptors (Boer *et al*., 1995).

MRZ does not inhibit the reuptake of serotonin or noradrenaline, nor does it inhibit monoamine oxidase activity, these properties differentiate it from several other classes of antidepressant drugs (Pinder, 1997a). In theory, blockade of the 5-HT_2 and 5-HT_3 receptors by MRZ could reduce the likelihood of some serotonergic

adverse effects associated with the nonselective serotonin receptor activation of SSRIs and venlafaxine (e.g., restlessness, nausea and sexual dysfunction) (Pinder, 1997a; 1997b) and this appears to be supported by tolerability data from clinical trials. The mechanism of action of MRZ therefore also incidentally causes pain reduction because the descending serotonergic pathways can inhibit nociceptive signaling via 5-HT$_1$ receptor activation (Fig. 1). Specifically, activation of 5-HT$_{1A}$ receptors inhibits the excitability of spinothalamic projecting neurons and excitatory (i.e., pain facilitatory) interneurons (Benarroch, 2008). Similarly, 5-HT$_{1B/D}$ receptor activation is antinociceptive through inhibition of neurotransmitter release from primary nociceptive afferents (Benarroch, 2008). In contrast, descending serotonergic pathway activation can promote nociceptive transmission by activating 5-HT$_{2/3}$ neurons (Benarroch, 2008; Zeitz *et al*., 2002).

In addition to its antidepressant effect, MRZ has a number of other pharmacodynamic effects. For example, blockade of 5-HT$_2$ receptors is associated with improvement in sleep quality (Pinder, 1997a), indeed, MRZ improves the quality and duration of sleep and unlike SSRIs, does not suppress rapid eye movement sleep (Aslan *et al*., 2002; Winokur *et al*., 2003; Shen *et al*., 2006). Although the initial dose of MRZ can cause psychomotor impairment (affecting driving ability), this is not sustained during continuing treatment (Ridout *et al*., 2003; Wingen *et al*., 2005). Interestingly, unlike reuptake inhibitors which can increase cortisol levels, (Schule *et al*., 2003) MRZ suppresses the secretion of cortisol.

The biotransformation of MRZ occurs primarily via the cytochrome P450 enzyme system in humans. MRZ is predominantly metabolized to 8-OH mirtazapine (8-OH) and to Desmethylmirtazapine (DMR) (Fig. 2). The former metabolite has no pharmacological effect, while DMR has been estimated to contribute 5-10% of the total pharmacodynamic activity of the drug (Delbressine *et al*., 1998).
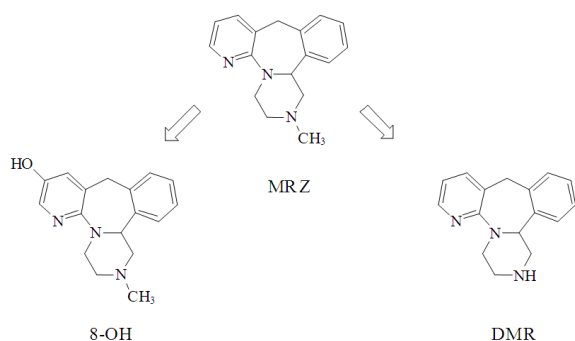

Fig. 2: Molecular structure of MRZ and its metabolites DMR and 8-OH

Recently, MRZ has been tested in cats (Quimby *et al*., 2011), dogs (Giorgi and Yun, 2011) and horses (Rouini *et al*., 2012). MRZ orally administered in the dose range (1.88-3.75 mg/cat day) caused significant polyphagia in cats, this pharmacokinetic behaviour is different to that of human beings. In canine species, MRZ orally administered (at about 1 mg kg^{-1}) showed a favourable pharmacokinetic profile (which is different to that in both cats and humans) compared to other CNS active drugs such as clomipramine (King *et al*., 2000), fluoxetine (Simpson *et al*., 2007) and trazodone (Gruen and Sherman, 2008). For these reasons, it was speculated (Giorgi, 2012) to be potentially useful for veterinary patients for treatment of anorexia and a wide range of anxiety-related conditions (Overall, 2000), for its antiemetic properties (due to antagonism of 5-HT$_3$ receptor) and as an analgesic in chronic and cancer-associated pain, due to its effects on both the noradrenergic and serotonic system (Bannister *et al*., 2009). Pharmacokinetics and metabolism have been reported to be largely variable among these species. Although MRZ has shown a good safety profile (better than other antidepressive drugs (Giorgi and Yun, 2011), caution should be taken in extrapolating doses from other species or humans.

It is likely to have additional applications for veterinary use, in particular, it has been suggested that its noradrenergic and serotonic system effects could be exploited for analgesic use (Bomholt *et al*., 2005). In this application, MRZ could represent a therapeutic option that results in a Non Steroidal Anti-Inflammatory (NSAIDs)-sparing effect, i.e., utilizing the noradrenergic and specific serotonergic analgesic effects to lower the required dose of NSAIDs. This combined use would reduce the likelihood and intensity of NSAIDs-induced side effects. This prospective application is highly attractive, especially in dogs and horses, species extremely susceptible to the adverse effects of NSAIDs.

A recent study effectively explained MRZ's effectiveness on pain in rodents (Kilic *et al*., 2011). It was demonstrated that MRZ had significant antinociceptive activity at the supraspinal level (hot plate test) and that antinociceptive activity was reduced when the dose was increased, explicitly, it has a biphasic activity. It is well established that serotonin has analgesic activity at the central level and analgesic activity at the peripheral level (Clauw and McCarberg, 2012). It was also demonstrated that MRZ has significant antinociceptive activity at the peripheral level (writhing test) and that the analgesic activity was reduced when the dose is increased. It is likely that this is associated with the emergence of peripheral analgesic

activity of serotonin when the dose is increased. It has been demonstrated that opioidergic mechanisms are also involved at these two levels (supra spinal and peripheral) (Giorgi, 2012). In contrast, MRZ had no antinociceptive activity at the central spinal level (tail clip and flick tests). Additionally, it has been demonstrated through the use of nitric oxide synthase inhibitors, that the NO and nitrergic pathways are not involved in the central analgesic activity of MRZ.

Interestingly, the antinociceptive effect of MRZ has been detected as soon as 30 minutes following drug administration. This supports the theory that the analgesic effect is independent of the antidepressive effect which takes 2 weeks for on-set. Despite this, there are some concerning data related to the oral bioavailability of this drug. This has been reported in approximately 3% of rats (Rouini and Giorgi, personal communication). As MRZ is predominantly administered orally and its bioavailability might vary widely among animal species, this data should be carefully evaluated in each species.

Given the complexity of pain and the variety of physiological mechanisms involved, single-agent regimens may not provide optimal analgesia for certain types of pain because they influence a limited number of therapeutic targets in the pain transmission and modulatory pathways (Raffa, 2006). Multidrug analgesic approaches take advantage of the complementary mechanisms of different drug classes to enhance analgesia and/or reduce side effects by lowering the required dose of one or more agents. The practice of combining MRZ with other analgesic agents is common and has been integrated into human clinical practice guidelines for the treatment of both acute and chronic pain (NIH, 1997; 2010; Dworkin *et al.*, 2007). Based on the information described in this study, MRZ is offered as a potential analgesic in veterinary species in a multidrug analgesic approach rather than as a single active ingredient. Further studies need to be carried out before its employment in clinical practice however.

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