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Ground-Breaking TRNA Therapy

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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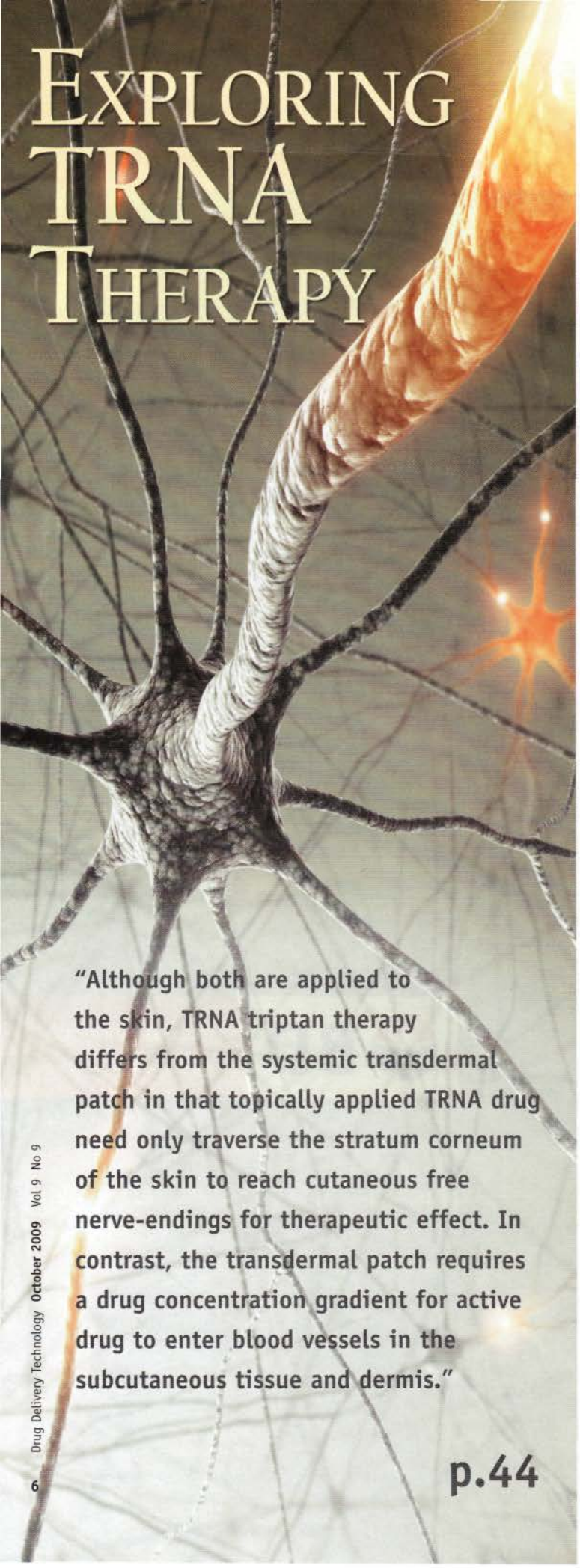

Exploring TRNA Therapy

"Although both are applied to the skin, TRNA triptan therapy differs from the systemic transdermal patch in that topically applied TRNA drug need only traverse the stratum corneum of the skin to reach cutaneous free nerve-endings for therapeutic effect. In contrast, the transdermal patch requires a drug concentration gradient for active drug to enter blood vessels in the subcutaneous tissue and dermis."

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TOPICAL DELIVERY

Topical Regional Neuro-Affective (TRNA) Therapy: Novel Ground-Breaking Triptan Drug Delivery for Treating Migraines

By: Ronald Aung-Din, MD

INTRODUCTION

Current short-comings in triptan therapy for migraine may now be overcome by the concept of topical regional neuro-affective (TRNA) therapy. This novel, proprietary (European Patent No. 1 435 945, granted Febraury 2008) triptan delivery is unique in providing therapeutic benefit while avoiding both systemic and cerebral blood. Drug blood levels are unnecessary as therapeutic effect is achieved by direct serotonin agonist (triptan) action on unmyelinated cutaneous free nerve-endings below the skin surface (stratum corneum) at the back of the neck (Figures 1 and 2).[1]

There exist free nerve-endings in the skin at the upper posterior cervical region (the back of the neck at the hairline, BONATH) as components of peripheral nerves of the region. These comprise branches of cervical nerve roots, C1-C4, which constitute the tract and nucleus of the Spinal (Caudal) Nucleus of the Trigeminal Nerve System (TNS), the Migraine Generator responsible for the migraine process within the cervical cord and brainstem. Roughly estimated, there is in the order of hundreds of thousands to millions of free nerve-endings in the approximate 12- to 14-cm square area of this anatomy that feedback to the trigemino-cervical neural complex.[2-4,9]

MIGRAINE PATHOPHYSIOLOGY & NEUROANATOMY

To appreciate TRNA technology, review of migraine pathophysiology and the region's neuroanatomy is in order (Figure 3). Migraine is believed the result of neuronal hyperexcitability within TNS. TNS provides pain and sensory input from the face, head and neck, sinus cavities, and intracranial dura and vessels. Migraine may be triggered by disturbances within these peripheral TNS components with subsequent involvement of central structures, resulting in typical symptoms of an attack. Certain odors or irritants stimulating the sinuses, neck muscle tension, changes in barometric pressure, sleep loss, stress, and other triggers can precipitate migraine. As TNS and other CNS structures become involved, head pain, nausea, and light and noise sensitivity become prominent. Cutaneous allodynia or unpleasant sensations of the skin affecting the face, scalp, and back of the neck is an early indication of the start of migraine. These symptoms represent neural irritation at the cutaneous free nerve-ending level within peripheral components of TNS.[3-6]

Triptans, as serotonin agonists, are thought to treat migraine symptoms by inhibiting neural transmission to central TNS structures and down-regulating neuronal hyperexcitability within TNS. Other events include dural vascular constriction with reduced permeability and diminished chemical inflammation. TRNA therapy allows expeditious triptan TNS down-regulation through direct peripheral afferent neural input from cutaneous free nerve-endings. This feedback down-regulation of CNS efferent neural output through peripheral afferent input activation is the same as in vagal nerve stimulation (VNS) for the treatment of seizures, headache, and depression. As CNS efferent activity is modulated, clinical symptoms of neuronal hyperexcitability as seizures or migraine are reduced.[7]

In addition to that by TNS, CNS afferent input from cutaneous free nerve-endings from BONATH is provided by the vagus nerve and the sympathetic nervous system through cervical neural connections within the soft tissues of the neck via vagal and sympathetic ganglia. The result is afferent neural input from skin at BONATH to TNS and other CNS structures involved with the migraine process providing enhanced feedback attenuation of clinical symptoms. The CNS and skin are both derived from the same embryological tissue (neuroectoderm), accounting for the rich neural connections between these two areas.

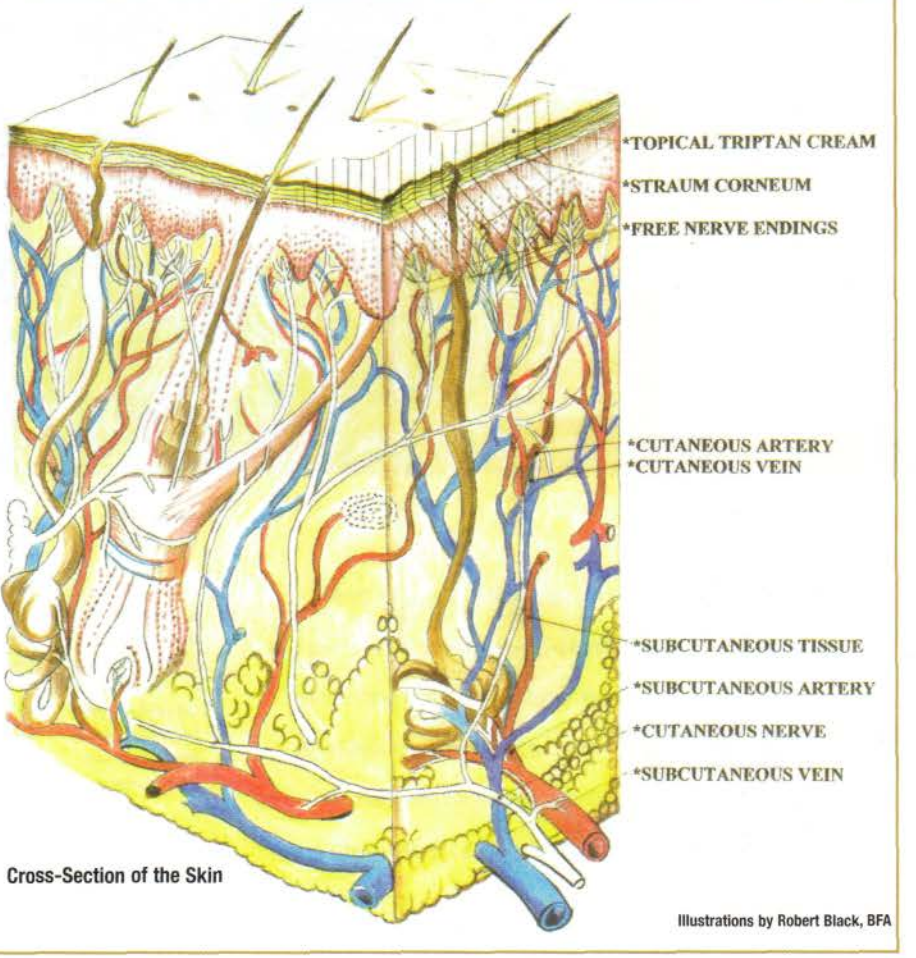
From the viewpoint of mechanism, TRNA may be seen as a combination of VNS and botulinum toxin (Botox) injection. TRNA is similar to VNS in functioning through afferent neural activation. Like Botox injection, TRNA drug action takes place at the peripheral

neural synapse. However, in contrast to VNS where surgical isolation of the vagus nerve at the anterior neck is required for direct afferent stimulation, cutaneous free nerve-endings below the skin surface at BONATH are utilized in TRNA for the same purpose. While Botox effect is at the neuro-muscular junction; in TRNA, it is at the sensory neuron receptor level.[8,9]

MIGRAINE: EXTENT OF THE PROBLEM & CURRENT TRIPTAN THERAPY

Despite significant advances in the understanding and treatment of migraine, a therapeutic void exists. Notwithstanding their efficacy and impact on migraine therapy, short-comings are apparent with triptans. Cost, tolerability, and overall acceptance contribute to the fact that much of the migraine population continues to rely on OTC products. Worldwide triptan use has not been as expected with seven same-class drugs on the market. The belief among some migraine sufferers is: considering the high cost of triptans, until the availability of something significantly more effective, safer, and convenient to justify change, OTC products are adequate. As migraine is not life-threatening but temporarily disabling, that logic seems difficult to argue.[1,8,10] Migraine headache affects some 28 million individuals in the US. The disorder is estimated to occur in 15% to 18% of women and 6% to 8% of men. Over 10% of the world population is afflicted by this medical condition. The World Health Organization (WHO) Task Force on Headache ranked migraine as one of the most disabling of chronic conditions; with attacks equating in disability to quadriplegia, psychosis, and dementia. Affected individuals are often young, productive, and in the prime of their lives; implying significant socio-economic impact.[11,12]

FIGURE 1



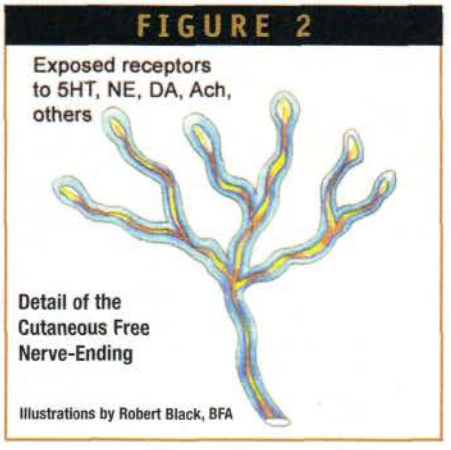
Cross-Section of the Skin

Illustrations by Robert Black, BFA

Introduced in the 1980s, triptans were developed to abort migraine attacks through their specific serotonin agonist action. They proved highly effective and significantly altered the approach to migraine treatment. With triptans, migraineurs were enabled to treat headaches without the need to see a doctor or go to the emergency room. Injections and treatments requiring healthcare professionals had been the usual practice for severe episodes. Patients were now capable of aborting attacks within a reasonably short (30 to 60 minutes) period of time and return to a relatively functional status. There was freedom to deal with migraine without the constraints of the healthcare delivery system.[7]

The success of triptans as a class was evidenced by six additional entries to market

FIGURE 2



after the first triptan, sumatriptan (Imitrex®): almotriptan (Axert®), frovatriptan (Frova®), zolmitriptan (Zomig®), naratriptan (Amerge®), rizatriptan (Maxalt®), and eletriptan (Relpax®). Sumatriptan is currently available as a tablet or in combination with the NSAID naprosyn (Treximet®), nasal spray, and subcutaneous injection. The other triptans are tablets except zolmitriptan, which also comes as nasal spray. Rizatriptan and zolmitriptan are available as plain or orally dissolvable tablets (ODTs).[1,13,14]

WHAT MIGRAINEURS WANT

In repeated surveys of migraine patients, rapid pain and symptom relief leads desire from therapy; followed by absence of recurrence, tolerability, convenience, and cost. The sumatriptan injection, although relatively rapid in onset, is associated with a higher incidence of side-effects and recurrence from drug bolus effect. The systemic and cerebral triptan effects of chest tightness, tingling of the face and extremities, lethargy, mental clouding, and fatigue are accentuated. Many also object to feeling a rush with the injection. Injections are considered invasive and viewed as inconvenient. Nasal spray is also generally not a preferred treatment for migraine. It may be associated with an objectionable taste as drug drips down the back of the throat.[10,15,16]

The pill is the most used form of triptan. However, the oral route may not be the most appropriate considering the clinical and pathological peculiarities of migraine. In addition to prominent head pain, significant gastrointestinal (GI) symptoms may occur during a migraine attack: nausea, vomiting, diarrhea, indigestion, and bloating. Patients are reluctant to take an oral drug when experiencing significant nausea and vomiting. Further, when vomiting occurs after pill ingestion, the question of repeating a dose arises. GI transit is impaired during the migraine process, delaying absorption of oral drugs. Studies also indicate absorption of oral triptans may be delayed by the presence of food in the digestive tract. Some orally ingested triptans are significantly metabolized by hepatic first-pass, affecting eventual drug blood levels. In the case of sumatriptan (Imitrex), nearly 85% of an oral dose is lost through hepatic first-pass metabolism.[17]

THE PROBLEM WITH SYSTEMIC DELIVERY OF TRIPTANS

All current triptan delivery relies on eventual presence in systemic and cerebral blood for therapeutic effect. Side effects are related to their presence in the circulation. Symptoms of chest tightness and numbness and tingling of the lips and extremities may be confused with those associated with more serious heart disease. This is further complicated by the fact that triptans have been demonstrated to cause vasocontriction. As a class, they are contraindicated with coronary artery disease, Prinzmetal's angina, and uncontrolled hypertension. They are likewise not advised in complicated migraine varients, such as hemiplegic and basilar migraine as these sub-types are associated with cerebrovascular vasocontriction and potential for stroke.[15-17]

The opinion of some headache experts is that overall triptan use has been limited by the potential for adverse events. Physicians are particularly reluctant to prescribe this drug class to older patients. Cardiac clearance may be recommended for such individuals prior to triptan use.[15,16]

IMPROVING TRIPTAN EFFECTIVENESS

In consideration of current limitations in triptan therapy, measures have been taken to enhance therapeutic benefit and widen use. To improve effectiveness of the plain sumatriptan tablet, it has been combined with the non-steroidal anti-inflammatory agent (NSAID), naprosyn (Treximet, GSK). NSAIDs are thought to block TNS synaptic central transmission. As non-selective cyclo-oxygenase (COX) inhibitors, the synthesis of prostaglandin, essential in the inflammatory component of migraine, is thought to be prevented.[1]

Studies are also underway with a transdermal sumatriptan patch (NuPathe) in an effort to maintain prolonged therapeutic blood levels of drug. However, with sustained triptan blood levels, issues with side effects and tolerability remain.[18]

THE UNIQUE MECHANISM OF TRNA TRIPTAN THERAPY

The author has applied triptans (eg, sumatriptan/Imitrex and frovatriptan/Frova), which are formulated as cream (12.5 mg sumatriptan in 0.5 ml) compounded in a dermal penetration-enhancing medium, to the BONATH of human patients. Through direct

effect on serotonin receptors of cutaneous free nerve-endings, afferent neural input is provided to TNS, effectively aborting the migraine process. As drug effect is achieved through neural connections than by bloodstream; clinical benefit is realized rapidly (10 to 15 minutes) and without the usual side effects of triptans.[19-21]

All current triptan delivery, whether injection, oral, nasal spray, or transdermal patch, ultimately require active drug in blood, exposing patients to side effects and other potential complications of systemic triptan therapy.[15,18]

TRNA DIFFERS FROM THE TRANSDERMAL PATCH

Although both are applied to the skin, TRNA triptan therapy differs from the systemic transdermal patch in that topically applied TRNA drug need only traverse the stratum corneum of the skin to reach cutaneous free nerve-endings for therapeutic effect. In contrast, the transdermal patch requires a drug concentration gradient for active drug to enter blood vessels in the subcutaneous tissue and dermis. These are at relative greater distance from the skin surface than the free nerve-endings (Figure 1). Further, after entry into the bloodstream, drug is required to be transported to the brain through cardiac output. As active drug is found in both systemic and cerebral blood, drug effect is not isolated to areas of migraine pathology, and extraneous effects are encountered. In contrast, in TRNA therapy, specific TNS pathways are affected through afferent neural connections from cutaneous free nerve-endings and upper cervical nerve roots. As therapeutic response is determined by rate of neural impulse than blood flow, clinical benefit is realized more rapidly with TRNA triptan delivery.[5,6]

TABLE 1

TRNA Versus Systemic Delivery (oral, injection, transdermal patch)

TRNA	Systemic
Direct affect on CNS through free nerve-endings and peripheral nerve connections.	Relies on therapeutic drug blood levels at CNS target sites.
Not rely on dermal, systemic, or cerebral blood flow for effect.	Drug enters systemic blood for effect after delivery by injection, patch, or as pill.
Rapid and prolonged drug effect as regional administration allows high tissue saturation of drug.	Therapeutic effect dependent on GI absorption, hepatic first pass, cardiac output, and cerebral blood flow.
Side-effects minimized without drug in systemic and cerebral blood.	Prone to systemic and CNS side effects.
Drug-drug interactions and metabolism/excretion negligible: may be considered "green."	Interactions with concomitant drugs and issues of metabolism and excretion.
Mechanism: analogous to electrical capacitor with charge build-up and discharge.	Mechanism: diffusion across concentration gradients and analogous to filling a reservoir to achieve a therapeutic level --- fluid dynamics.

The analogy is of an electrical capacitor discharging after charge build-up (TRNA) compared to a fluid reservoir filling to a required therapeutic level (transdermal patch). Finally, with TRNA therapy, the specific placement of active drug, as acute use single-dose cream or sustained delivery patch, at the BONATH is key in capitalizing on the unique relationship of the region to TNS with respect to providing important afferent input. On the other hand, the systemic transdermal patch may be placed anywhere on the body as anatomical location is irrelevant to its mechanism of action. As dilution in blood is not a consideration with topical regional delivery, active drug dose requirements are also much lower (Table 1).[18]

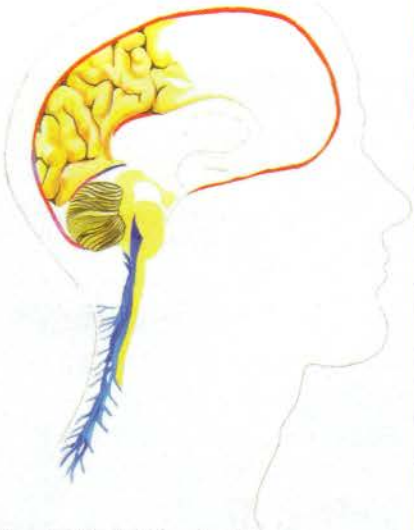
As alluded, the principles of TRNA therapy may also be applied to a sustained release patch and other depot drug delivery systems administered to the BONATH, with the only requirement of availing active drug to the cutaneous free nerve-endings for therapeutic effect. Conditions characterized by persistent, recurrent headaches, such as menstrual migraine, would benefit from such applications.

TRNA technology may be considered environmentally friendly or green. With negligible to no active drug in blood, there is lack of metabolism and excretion into the environment. Likewise, there is no concern for drug-drug interactions with concomitant medications.

CLINICAL EXPERIENCE WITH TRNA TRIPTAN THERAPY

In the 8 years of development, sumatriptan and tizanidine TRNA therapy has been used in over 300 patients, leading to the publication of five papers at

FIGURE 3



Trigemino-Cervical Complex: The Neuroanatomical Basis of Migraine

International Headache and Clinical Research Meetings. Observations with TRNA in established migraineurs with prior traditional triptan use indicated onset of relief of headache and other migraine symptoms occurred in the majority within 10 minutes of topical sumatriptan (12.5 mg sumatriptan) compounded cream application. Headache response (moderate/severe to mild/none) was achieved in the majority within 30 minutes; less than 10 minutes in 30%. No significant side effects, in particular triptan effects, were noted.[19-21]

Topical tizanidine (Zanaflex) alone or in combination with sumatriptan has also been investigated with TRNA technology in both migraine and tension-type headache with similar positive results. Studies are currently underway to evaluate the utility of this novel delivery process with other CNS-active drugs. The dopamine agonist apomorphine is being studied in Parkinson's disease and essential tremor with initial findings of significant clinical response to TRNA therapy.[22-24]

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BIOGRAPHY

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