

PROKARIN™

Prokarin™* is a compound “off-label” prescription transdermal medication. The two active ingredients in Prokarin™ are histamine phosphate and caffeine citrate. Prokarin™ is not FDA approved for the indication of multiple sclerosis.

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The information contained in this packet is not intended to cover all possible uses, directions, precautions, drug interactions, or adverse effects. This information is generalized and is not intended as specific medical advice. The FDA has not evaluated this information. This product is not intended to diagnose, treat, cure or prevent any disease.

* Prokarin™ was formerly known as “Procarin”. The revised spelling was adopted to avoid potential conflicts with other existing trademarks.

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HYPOTHALAMUS / HISTAMINE CHAIN REACTIONS

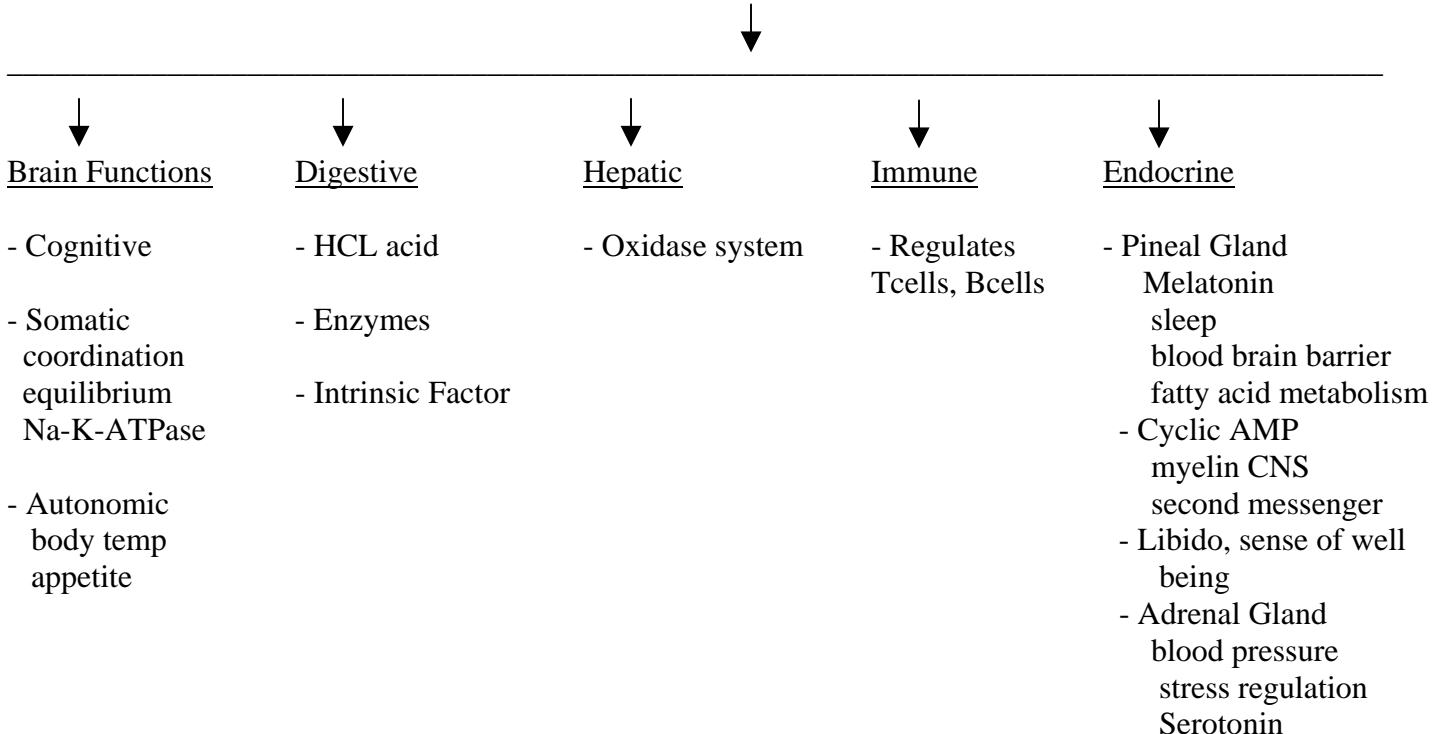
Hypothalamus:

1. Major relay station for the brain, to the brainstem and the spinal cord.
 - a. Nerve synapse junctions from:
 - cerebellum involved in coordination and equilibrium
 - cortex involved in cognitive functions
2. Links the nervous system to the endocrine system
 - a. Adrenal cortex gland function
 - blood pressure, water balance, cortisol production, steroid hormone production
 - b. Thyroid gland function
3. Essential in maintaining the waking state.
4. Appetite regulation
5. Sense of well being
6. Body temperature regulation

Histamine via H2 receptor stimulation:

Major neurotransmitter in the hypothalamus and regulates other neurotransmitters as well

CHAIN REACTIONS DEPENDENT ON H2 RECEPTOR STIMULATION



Literature Review

Vitamin B12

Vitamin B12 (cobalamin) is essential in the production and maintenance of myelin throughout the nervous system (Baer & Williams, 1992). It plays an important role as a cofactor in the metabolism of lipids and carbohydrates (Sandyk & Awerbuch, 1992). Impairment of lipid metabolism may interfere with the formation of the lipid portion of the myelin sheath resulting in demyelination (Baer & Williams, 1992).

Vitamin B12 absorption is dependent on the presence of intrinsic factor in the small intestine (Baer & Williams, 1992). Schilling's tests were performed on 49 multiple sclerosis (MS) patients and the results were abnormally low in 11.9% of the subjects (Gupta, Ingegno, Cook, & Pertschuk, 1977). Vitamin B12 is transported to the liver from the gastrointestinal tract where it is stored and slowly released. The transport of vitamin B12 is associated with two carriers, transcobalamin II and R binder protein (Baer & Williams, 1992; Kira, Tobimatsu, & Goto, 1994). A study by Kira et al (1994) showed some MS patients have a decreased serum unsaturated R binding capacity, while a study by Reynolds, Bottiglieri, Laundry, Crellin, & Kirker (1992) showed elevated serum R binding capacities in MS patients. Vitamin B12 is a water soluble vitamin, so perhaps vitamin B12 must be bound to one of the carrier molecules, transcobalamin II or the R binder protein in order to cross the blood-brain barrier. The blood-brain barrier is impermeable to water soluble drugs unless bound to a carrier molecule (Baer & Williams, 1992). Perhaps the binding of vitamin B12 to its carrier molecule involves the hepatic oxidase system and histamine H₂ which is discussed later. A study by Nijst, Wevers, Schoonderwaldt, Hommes, & de Haan (1990) revealed the median cerebrospinal fluid (CSF) vitamin B12 level to be significantly lower than the serum vitamin B12 level in 58 patients with definite MS. The CSF level of vitamin B12 was significantly lower in the MS subjects than in the other 235 subjects who had a neurological disease other than MS. These findings may correlate with the fact that the sclerotic lesions characteristic of MS are almost exclusively found in the CNS.

Numerous studies have cited that macrocytosis is common in patients with multiple sclerosis (Crellin, Bottiglieri, & Reynolds, 1990; Reynolds et al, 1992; Goodkin et al, 1994). The etiology of the macrocytosis is unknown, but it has been speculated to be related to vitamin B12 metabolism, transport, or binding, perhaps again involving the hepatic oxidase system. Various studies have revealed conflicting findings as to whether vitamin B12 deficiency is significant in patients with MS, although mild macrocytosis is prevalent (Reynolds et al, 1992; Crellin et al, 1990; Goodkin et al, 1994). A study by Goodkin et al (1994) concluded that only 19.4% of the MS subjects had vitamin B12 levels less than 301 pg/ml. It was not established in this study if the subjects were in remission or exacerbation or by what means their diagnosis of MS had been determined. Furthermore, the study states that 9 of the patients in the study population were diagnosed with chronic progressive idiopathic myelopathy, but that none of these individuals had any sclerotic lesions detected via spine and brain magnetic resonance imaging scans. In contrast to the Goodkin et al (1994) study, Reynolds et al (1992) showed significant vitamin B12 deficiency in 31% of the MS subjects with levels less than 200 pg/ml. The subjects in this study had been diagnosed as having definite MS on the basis of multiple fluctuating lesions in the CNS detected via magnetic resonance imaging and the detection of oligoclonal bands in the CSF. But this study also did not identify if the subjects were in remission or exacerbation.

The study by Kira et al (1994) showed that massive doses of vitamin B12 improved the multimodality evoked potentials in patients with chronic progressive MS. These findings reflected an improvement in the demyelinating lesions on the afferent pathways.

Adenosine Monophosphate / Cyclic AMP

Cyclic AMP stimulates the synthesis of myelin components by oligodendrocytes and Schwann cells (Anderson & Miskimins, 1994; Lyons, Morell, & McCarthy, 1994) as well as being a necessary second messenger involved in cell activity. Studies have shown that oligodendrocytes, the myelin producing cells of the CNS, will undergo self induced degeneration in the absence of cyclic AMP.

These degenerating cells will again become viable and capable of synthesizing myelin if treated with cyclic AMP (Kim, 1990; Sato & Yu, 1991; Raible & McMorris, 1993; Anderson & Miskimins, 1994; Lyons et al, 1994). The Schwann cells, the myelin producing cells of the peripheral nervous system, become dormant but do not degenerate in the absence of cyclic AMP (Lyons et al, 1994). This may account for the myelin plaques being isolated to the central nervous system. A study by Hartikka, Staufenbiel, & Lubbert (1992) revealed that increased intracellular levels of cyclic AMP protect mesencephalic dopaminergic neurons from stress induced degeneration. Perhaps the findings of this study correlate with the fact that stress often induces exacerbations of symptoms in MS patients, in fact MS patients have inadequate cyclic AMP production. Adenosine and its derivatives, such as, adenosine monophosphate was proven to be a potent stimulator of cyclic AMP formation in brain tissue (Phillis & Barraco, 1985). Although no documentation was found indicating that any research studies have been performed using adenosine monophosphate in MS patients, Dr. Bjork, in his book "Multiple Sclerosis and How I Live With It", cites the beneficial effects of parenterally administered adenosine monophosphate and vitamin B12 in many MS patients (1978).

Histamine H2

Histamine H2 producing cell bodies are located in the posterior hypothalamus. Histamine is a major neurotransmitter and neuromodulator in the central nervous system (Nowak, 1994). Histamine H2 receptor sites are located in the CNS, the hepatic oxidase system, peripheral lymphocytes, and the parietal cells in the intestinal lining. Histamine H2 in the gastric system stimulates the parietal cells to secrete hydrochloric acid and intrinsic factor. Thus, the presence of histamine H2 is necessary for the absorption of vitamin B12 from the intestinal tract. The binding of histamine H2 to receptors in the intestinal lining also stimulates the secretion of gastrin and pepsin (Baer & Williams, 1992). Thus, histamine H2 is directly involved with the digestion of protein, fats, and carbohydrates. Curiously, a study by Gupta et al (1977) revealed microscopic fat in 41.6% of MS patients whose stools had been randomly screened using Sudan III stain.

Also, 40.9% of the MS subjects showed undigested meat fibers in the stools. This study also identified the presence of a measles viral antigen in the nuclei of epithelial cells in all of the jejunal biopsies performed in 40 MS patients. These findings by Gupta et al (1977) were supported by Yarosh & Kanevskaya (1992) study in which histological abnormalities were identified in all the gastric mucosa biopsies of 32 MS patients. Yarosh & Kanevskaya (1977) also established a high level of blood histamine in those MS patients whose disease length was less than five years, and a low level of blood histamine in those whose disease length was greater than five years. Curiously, in the majority of MS cases the onset of the disease is characterized by attacks and remissions during the first five to ten years. Generally after ten to twenty years, some degree of chronic disability is present (Bjork, 1978). Perhaps an explanation for this phenomenon is that as an organ is damaged it releases its enzymes into the blood, resulting in elevated serum levels. As the organ progressively degenerates, less and less of its enzymes are released into the blood (Wilson & Smith, 1992). Perhaps a slow measles virus lies dormant in the histamine H₂ producing cells in the posterior hypothalamus until some stressor triggers the latent virus to become lytic. This may result in the degeneration of the histamine H₂ producing cells and may account for the histological changes in the gastric mucosa, abnormally high levels of measles antibodies in the cerebral spinal fluid, the decrease in serum histamine levels over time, and the chronic progression of the disease.

Histamine H₂ has receptors in the peripheral lymphocytes which are concerned with the regulation of T-cells and B-cells (Baer & Williams, 1992). Beta-adrenergic receptor density on lymphocytes is indirectly proportionate to the availability of histamine H₂. Studies show that an increase in histamine H₂ results in a decrease in the density of beta-adrenergic receptors on lymphocytes (Galant & Britt, 1994; Mita, Yui, & Shida, 1983). The significance of these findings to multiple sclerosis is that beta-adrenergic receptor density is two to three times greater than normal values in patients with progressive MS or in an exacerbation. The beta-adrenergic receptor density was within normal values in MS patients who were in remission (Karaszewski, Reder, Maselli, Brown, & Arnason, 1990; Zoukos, Leonard, Thomaidis, Thompson, & Cuzner, 1992).

Furthermore, a study by Dziuba, Frolov, & Peresadin (1993) indicated that during exacerbation, patients with MS had marked T-lymphopenia.

The CNS has histamine H₂ receptors that when stimulated increase cyclic AMP production as evidenced by the Nowak & Sek (1994) study that showed histamine H₂ to be a powerful stimulator of cyclic AMP production in the chick pineal gland. The activity of the pineal gland is regulated by histamine H₂. Pineal calcification has been found in 100% of MS patients studied (Sandyk & Awerbuch, 1991). Exogenous histamine H₂ greatly increases endogenous cyclic AMP accumulation and moderately increases melatonin secretion. The effect of histamine H₂ to stimulate the increase in the production of cyclic AMP is enhanced by the presence of a phosphodiesterase inhibitor (Nowak & Sek, 1994). Methylxanthine agents, such as theophylline, theophylline derivatives, and caffeine, inhibit phosphodiesterase, the enzyme that breaks down cyclic AMP. Caffeine is the medication of choice because it has a longer half-life, less untoward side effects, and a wider therapeutic index (Baer & Williams, 1992). The pineal gland produces melatonin as well as cyclic AMP. Melatonin levels are abnormally low in MS patients (Sandyk & Awerbuch, 1992). Melatonin is essential in fatty acid metabolism and there is a high incidence of hypercholesteremia in MS patients (Sandyk & Awerbuch, 1994) perhaps due to low levels of melatonin secondary to pineal dysfunction as a result of deficient histamine H₂ stimulation. Melatonin is involved in the circadian rhythm. Melatonin regulates the activity of serotonin neurons in the brainstem. Inhibition of melatonin results in the cease firing of the serotonergic neurons during REM (rapid eye movement) sleep which results in sleep atonia associated with REM sleep. MS patients experience cataplexy which is physiologically and pharmacologically similar to sleep atonia during REM sleep (Sandyk, 1995). Brain histamine H₂ is also involved in neuroendocrine regulation, thermoregulation, water intake, and analgesia (Ghi, Blengio, Ferretti, & Portaleone, 1992). Histamine H₂ stimulates the synthesis of the neurotransmitter serotonin.

Serotonin and histamine H₂ stimulate cyclic AMP synthesis. Histamine H₂ either alone or in combination with serotonin and cyclic AMP maintains the integrity and the permeability of the blood-brain barrier (Sharma, Nyberg, Cervos-Navarro, & Dey, 1992). As mentioned earlier, perhaps the low level of vitamin B₁₂ in the CSF of MS patients is associated with a low histamine H₂ serum level resulting in a decrease in the permeability of the blood-brain barrier.

Histamine H₂ plays an important role in modulating stress. Production of histamine H₂ is increased with stress (Ghi et al, 1992). The study by Sharma et al (1992) showed that histamine H₂ is an important modulator in heat-stress. Perhaps there is a correlation between these findings and the fact that episodes of relapses in MS patients is often precipitated by stress, such as pregnancy, infection, emotional stress, heat, or physical injury (Ozuna, 1992). Furthermore, histamine H₂ stimulates the increase of serum corticosterone levels, especially adrenocorticotropin hormone (ACTH) following mild stress (Ghi et al, 1992). Perhaps this explains why ACTH and prednisone are often helpful in decreasing symptoms in acute exacerbations, but do not necessarily reduce the long term neurological deficits of MS (Ozuna, 1992; Kelley & Smeltzer, 1994). Perhaps an explanation for this is that ACTH and corticosteroids decrease the inflammatory response triggered by myelin degeneration which may be induced by the lack of vitamin B₁₂ and cyclic AMP secondary to a lack of histamine H₂.

Etiology

The etiology of MS is unknown but the most currently accepted theory is that a genetic predisposition to a possible viral factor may underlay MS (Morgante, Madonna, & Pokoluk, 1989). This theory of a genetic predisposition may explain, in part, the higher incidence of MS in women than men, and that the disease is more prevalent in Caucasians than Blacks or Asians (Ozuna, 1992). The possible viral factor addressed in this theory may explain why the incidence of the disease is highest in the temperate zones of the world between 45 degrees and 65 degrees latitude (Ozuna, 1992). Antibodies to the measles virus are higher than normal levels in the serum and CSF of MS patients (Kelley & Smeltzer, 1994). This theory is further supported by the fact that Betaseron, an interferon-beta which is an antiviral, has proven to be effective in reducing the frequency and severity of exacerbations in patients with relapsing-remitting MS. Betaseron has also shown to decrease the size of the sclerotic plaques in the CNS (Kelley & Smeltzer, 1994). A study by Wolfgram &

Tourtellotte (1992) showed that the amino acid composition of myelin in MS patients was quite different than the amino acid composition of immunoglobulins thus ruling out the binding of antibodies to the myelin. Thus, the antiviral action of Betaseron must be targeted to other tissue cells rather than myelin cells. These findings may also disprove the theory of an autoimmune etiology. Perhaps MS develops as a result of a slow measles virus affecting the histamine H2 producing cells and that the demyelination of the CNS is a complication of this process secondary to the lack of histamine H2, vitamin B12, and cyclic AMP.

Summary

Vitamin B12 and cyclic AMP are essential for the production and maintenance of myelin, and that vitamin B12 and cyclic AMP are dependent on the availability of histamine H2. Although some studies have resulted in conflicting findings in the serum levels of vitamin B12 in MS patients, all studies verified decreased levels of vitamin B12 in the CSF of MS patients. There are no documented research studies indicating the use of adenosine monophosphate in MS patients, but there are some reports of MS patients benefiting from the conjunctive parenteral administration of adenosine monophosphate and vitamin B12. Studies have shown that the serum level of histamine H2 decreases to an abnormally low level as the length of the disease increases. Furthermore, studies have shown abnormal histological changes in the gastric mucosa of MS patients and that the measles viral antigen has been identified in the intestinal lining of MS patients. These facts and findings warrant the need for further research in identifying the effects of the transdermal application of histamine phosphate / caffeine in MS patients.

Facts Supporting the Histamine₂ (H₂) Receptor Theory

1. Histamine₂ (H₂) receptors are in the CNS, hepatic oxidase system, peripheral lymphocytes, and the parietal cells in the intestinal lining.
 - a. H₂ stimulates secretion of gastrin, pepsin, HCL, and intrinsic factor.
 - MS patients have microscopic fat and undigested meat fibers in their stools
 - Macrocytosis is common in MS patients. CSF B12 level is significantly lower than the serum B12 in MS patients. B12 is water soluble and must be bound to a carrier molecule to cross the BBB. H₂ regulates the permeability of the BBB by regulating the pineal gland.
2. Histamine₂ (H₂) regulates the activity of the pineal gland.
 - a. H₂ stimulates the pineal gland to produce cyclic AMP and melatonin.
 - b. Melatonin is important in immunomodulation and regulation of the integrity of the blood brain barrier.
3. H₂ is a major heat stress modulator for the body.
 - a. Heat worsens symptoms in MS patients.
 - b. Melatonin lowers body temperature.
 - c. Deficient H₂ receptor stimulation results in constriction of small diameter peripheral arteries.
4. H₂ stimulates the synthesis of serotonin and melatonin.
 - a. Melatonin regulates the activity of the brainstem serotonin neurons.
 - b. Low levels of serotonin and melatonin results in almost complete paralysis of striated muscles as in REM sleep.
 - REM stage of sleep occurs when melatonin is at the lowest level (immediately following a swing from high to low in the melatonin level).
 - MS patients often experience sleep atonia associated with REM stage of sleep.
 - c. MS patients have decreased melatonin secretion.
5. Melatonin levels increase during pregnancy and rapidly fall postpartum.
 - a. MS patients have a decrease in symptoms during pregnancy, but an increase in symptoms in the first months of postpartum.
6. MS patients have a high serum level of histamine whose disease length is < 5 years and a low level of histamine in those whose disease length is > 5 years.
 - a. In majority of MS cases, the onset of the disease is characterized by attacks and remissions during the first 5 – 10 years and generally after the 10 years some degree of chronic disability is present.
7. H₂ is a stress modulator.

8. H₂ blockers antagonize the stimulatory effect of H₂ on cAMP production.
 - a. Over dosage of ranitidine can cause reversible blurred vision, gait disturbances, involuntary motor disturbances, leukopenia, and hypotension.
9. H₂ regulates T-cell and B-cell lymphocytes.
 - a. Beta adrenergic receptors on the lymphocytes is negatively proportionate to the availability of H₂. Increased H₂ results in decreased density of the receptors.
 - b. MS patients in exacerbation or chronic progressive MS have 2-3x > normal values in the density of the beta adrenergic receptors.
 - c. MS patients in remission have normal density values.
 - d. MS patients in exacerbation have marked T-lymphopenia.
10. Oligodendrocytes are the myelin producing cells in the CNS and Schwann cells are the myelin producing cells in the peripheral nervous system.
 - a. Schwann cells are dormant in the absence of cAMP.
 - b. Oligodendrocytes self degenerate in the absence of cAMP.
 - c. Sclerotic plaques are only in the CNS of MS patients.
 - d. H₂ is the most potent stimulator of the pineal gland to produce cAMP.
11. Exogenous H₂ greatly increases endogenous cAMP accumulation and moderately increases melatonin secretion.
 - a. Effects of H₂ are increased with a phosphodiesterase inhibitor, such as caffeine.
12. Pineal atrophy was seen in 100% of MS patients during acute exacerbation.
 - a. Weak electromagnetic fields stimulate pineal activity.
Improvement in symptoms in MS patients is seen within 24 hours after receiving picotesla electromagnetic fields.
13. H₂ stimulates the Na⁺ - K⁺ - ATPase at the post synaptic cleft.
 - a. Na⁺ - K⁺ - ATPase stimulation is necessary to induce the change in the ion gradient of the axon membrane so that an impulse can be carried down the nerve pathway.

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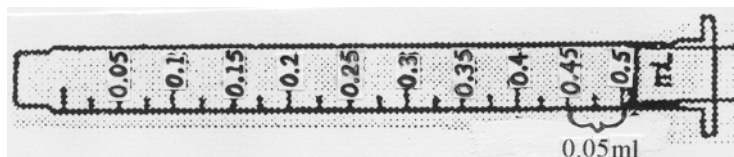
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HOW TO APPLY THE PROKARIN™* PATCH, ONE-PATCH A DAY APPLICATION

IMPORTANT NOTE: The Prokarin™-gel must be refrigerated at all times. When traveling carry Prokarin™ in an insulated carrier with ice packs. Do not freeze the Prokarin™-gel.

1. Make sure the skin is clean and dry. See the attached chart for appropriate sites to apply the patch.
2. Inspect the skin for any open areas or sores. Do not apply the patch to any areas that have a sore, crack in the skin, or open areas.
3. Apply a small amount of hydrocortisone cream 1% to the skin where the patch is to be applied. Gently rub the cream into the skin until it is completely absorbed and the area is dry.
4. Peel back the white paper backing on the adhesive patch until $\frac{3}{4}$ of the sticky adhesive side is exposed.
5. Apply 0.05ml (See the titration schedule for one-patch a day application) of the medication in the syringe to the middle portion of the exposed sticky side of the adhesive patch. The medication should be applied as a “glob” in the center of the patch.



6. Completely remove the adhesive patch from the white paper backing and apply the patch to the skin that has been prepared with the hydrocortisone cream. **Make sure there are no wrinkles in the patch and that all edges are well sealed to the skin.** If wrinkles occur, try applying the patch on the front of the thigh while the thigh muscle is flexed such as in a standing position or sitting with the leg extended out in front of you on a chair. Apply the patch horizontal on the thigh.
7. Apply the patch as prepared above in the AM and wear until bedtime. Remove the patch at bedtime. Gently rub any medication remaining on the skin or patch into the skin. **There should be about 25% of the medication left on the skin or patch when the patch is removed and this remaining medication should be as moist as the medication was when it was first applied from the syringe. If the remaining medication is flaked, clumpy, or caked, air got under the patch and this will affect the absorption of the medication.**
8. Be sure to rotate the sites where the patch is applied. Never apply the patch to the same site twice in 24 hours.
Note: If the temperature of the environment is greater than 85 degrees Fahrenheit, the patch may need to be applied twice a day under the direction of your doctor (Please consult with your pharmacist for instructions on a Two-Patch Application). A person with a higher metabolism, or experiencing increased mental or physical stress may need to increase the frequency of dosing under the direction of his or her doctor.
9. Repeat steps 1 through 8 every day.

Note: Do not get the patch wet. If the patch gets wet, remove the patch **immediately**, gently pat the area dry and apply a **new** patch at a **different** site following the above steps. Do not apply a heating pad over the patch site.

It may take several weeks after continual use to see a beneficial effect.

Precautions: If any sores develop on your skin or you experience any nausea, diarrhea, stomach pains, difficulty breathing, frequent headaches or a headache that does not resolve with acetaminophen, rapid pulse, or chest pain, remove the immediately and call your doctor.

Side Effects: Possible side effects of Prokarin™ use include: pain, tenderness, bruising, swelling, inflammation, or rash at the patch site, flushing, dizziness, headache, fainting, cyanosis (bluish coloring) of the face, hypotension, hypertension, pulse irregularities, rapid pulse, chest pain, dyspnea (difficult or painful breathing), abdominal discomfort, nausea, vomiting, diarrhea, increased urination, increase in symptoms of bursitis and tendonitis, burning or itching skin, nervousness, metallic taste, blurred vision, blood clots in arms or legs, may decrease blood sugars in diabetics, (use caution in patients with hypoglycemia), and severe allergic reaction that could result in shock, convulsions, and death.

Contraindications: Contraindicated in respiratory disorders (asthma, chronic bronchitis, emphysema, etc.), gastrointestinal ulceration, or concurrent use with some medications used to treat stomach or esophageal disorders (e.g. Zantac®, Tagamet®, Pepcid®, Axid®, ranitidine, cimetidine). Baclofen® (lioresal) and Zanaflex® may decrease the effectiveness of Prokarin™.

*Prokarin™ was formerly known as “Procarin™”. The revised spelling was adopted to avoid potential conflicts with other existing trademarks.

Suggested Titration Schedule for Prokarin, One-Patch a Day Application

0.2 mg of Histamine Phosphate / 100 mg Caffeine Citrate / 0.2 ml

Note: If the patient experiences subtle improvement in symptoms at any level in the titration schedule, then instruct the patient to remain at that level until the patient feels he/she has reached a plateau in symptom improvement, then continue the titration.

First 5 days use 0.05 ml qd (apply patch in AM and remove at bedtime)

Then days 6-10 use 0.1 ml qd (apply patch in AM and remove at bedtime)

Then days 11- 15 use 0.15 ml qd (apply patch in AM and remove at bedtime)

Then day 16 and on use 0.2 ml qd (apply patch in AM and remove at bedtime)

If the patient experiences an abrupt worsening during the first 5 days using 0.05 ml one patch per day, then instruct the patient to follow the titration schedule using 0.025 ml increments. See below: (Often these patients will not need to titrate the dose higher than 0.1 ml per day)

First 5 days use 0.025 ml qd (apply patch in AM and remove at bedtime)

Days 6-10 use 0.05 ml qd (apply patch in AM and remove at bedtime)

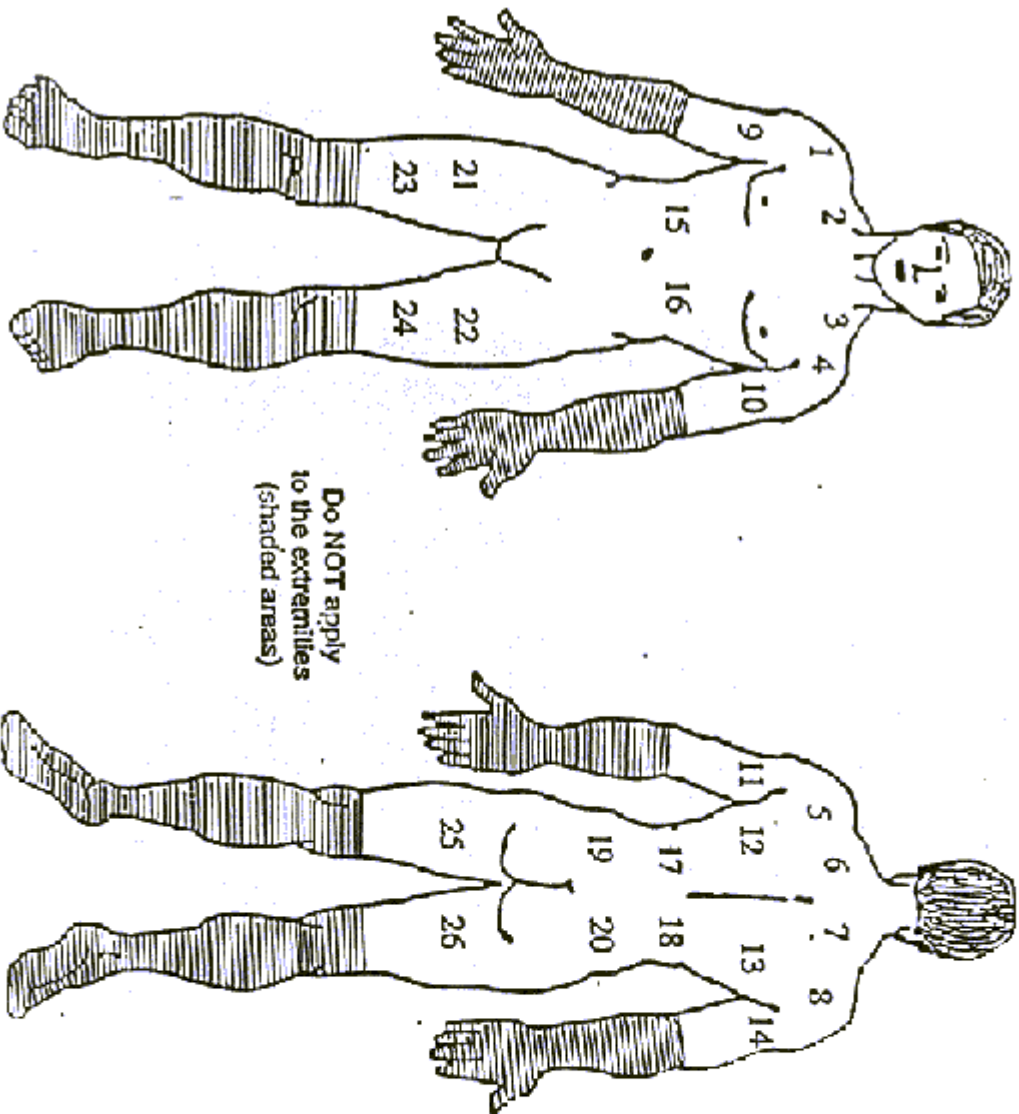
Days 11-15 use 0.075 ml qd (apply patch in AM and remove at bedtime)

Days 16 and on use 0.1 ml qd (apply patch in AM and remove at bedtime)

If at anytime during the titration, the patient experiences an abrupt worsening in symptoms, have the patient go back down to the next lower dose that was well tolerated. Instruct the patient to remain on this dose until he/she experiences a plateau or gradual worsening of his/her symptoms, and then have the patient continue with the titration schedule.

Some patients may experience the best benefit using two patches a day. If the patient experiences a worsening or increase in symptoms that persist throughout the afternoon or evening and these symptoms do not resolve after removing the patch instruct the patient to try two patches a day and continue to evaluate its effect. (Please see Suggested Titration Schedule for Two-Patch a Day Application).

TRANSDERMAL PATCH APPLICATION SITES



Do NOT apply
to the extremities
(shaded areas)

WASH HANDS BEFORE AND AFTER APPLICATION
Be sure to rotate application sites to prevent skin irritation
and reduce skin tears. Use at least 4 different sites.

Do NOT apply on the head and neck or below
the knees or elbows. Avoid the shaded areas on
the drawings. The front of the thighs are the
preferred sites of application (sites 21-24). Also
avoid skin folds, scar tissue, burned, cut, or
irritated areas.

The areas should be clean, dry and reasonably
hairless. If hair is likely to interfere with adhesion or
removal, it can be clipped, but NOT shaved.

Do not wet the patch wet. Contact with water may
result in skin damage at the site of application.



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