Current Concepts of Pharmacotherapy in Hypertension

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Transdermal Clonidine: Therapeutic Considerations

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Transdermal clonidine was approved by the US Food and Drug Administration in 1984 for the treatment of mild-to-moderate hypertension alone or in combination with a diuretic. Clonidine is released from the patch at a constant rate and thus displays a pharmacokinetic pattern not dissimilar to that of infusion therapy. Transdermal clonidine, like oral clonidine, is effective first- or second-line therapy for most forms of hypertension. More recently, transdermal clonidine has found alternative uses in the areas of smoking cessation, posttraumatic stress disorder, menopausal hot flashes, and alcohol and opiate withdrawal syndromes. The not infrequent development of a dermatitis, together with a substantially greater cost than oral clonidine, have been the major undoings for transdermal clonidine. (J Clin Hypertens. 2005;7:558–562) ©2005 Le Jacq Ltd.

Transdermal clonidine was approved by the US Food and Drug Administration in 1984 as a transcutaneous antihypertensive formulation that provides sustained drug delivery for up to 168 hours.[1,2] Transdermal clonidine therapy differs from conventional oral therapy in that blood drug levels remain constant throughout a 7-day dose interval, falling in a therapeutic range without the peaks and troughs of drug concentration seen with oral clonidine therapy.[3,4] Clonidine in this delivery system is better tolerated with respect to dry mouth and/or drowsiness.[4,5]

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www.lejacq.com ID: 4133

PHARMACOLOGY

In the first two (unpublished) clinical trials of the product, conducted in 1977 and 1978, 20 patients had two small circular patches, each measuring 1.6 cm^2, applied to the postauricular area. The patch was poorly adherent at this site for several of these patients and, in addition, after 2 weeks of therapy the blood pressure (BP) was less effectively controlled than it had been with prior oral clonidine treatment. This early experience led to studies using a larger patch (3.9 cm^2) applied to the outer surface of the upper arm in two studies carried out in the early 1980s. These studies were important for transdermal clonidine in that they provided insight into its differing absorption characteristics based on patch location.[6]

Of note, the plasma concentrations of clonidine have been determined following application of transdermal therapeutic systems to different parts of the body. The average clonidine concentrations in the patients studied were higher when the skin devices were applied to the chest or the upper arm than when applied to the thigh (Table).[7] For all sites, the Day 6 concentrations exceeded those

observed on the first day. This latter finding reflects the sequestering of drug within the stratum corneum during the early stage of treatment. The amount of drug administered is not governed by the size of the system reservoir, but instead depends on the contact surface area of the patch. As such, the size of a skin patch corresponds to the plasma concentrations attained during steady state treatment.

The clonidine transdermal therapeutic system consists of a 0.2-mm adhesive patch with a drug reservoir, a membrane that controls delivery rate, and a pliable backing (Figure). Transdermal clonidine is released from the patch at a constant rate and as such has an absorption pattern (zero-order kinetics) that mimics the circumstances of a sustaining infusion. The clonidine suspension in the reservoir ensures continous delivery provided that the reservoir remains at least 40% saturated. The transdermal system has been shown to contain this percentage of clonidine (at a minimum) for up to 9 days.[8]

Pharmacokinetic studies have demonstrated that after placement of a first patch, the clonidine (α_2 stimulant) in this delivery system takes 2–3 days to achieve therapeutic blood levels.[5] Initially after application, clonidine is rapidly released from the saturated adhesive layer within the first 8 hours. This initial flow of drug primes the skin in that a significant amount of drug is required to fix to skin proteins before it can be released into the blood stream. Upon removal of the patch, plasma levels remain constant on average for approximately 8 hours and thereafter decline over several days, with a plasma half-life of 21 hours. On discontinuation of transdermal clonidine, rebound and/or overshoot hypertension is uncommon, since residual drug in the skin functions in a depot-like fashion allowing for a gradual decline in clonidine plasma levels.[9,10]

BLOOD PRESSURE

Clonidine, given either orally or transdermally, has been an accepted standard for the treatment of hypertension. Transdermal clonidine is effective as monotherapy in BP reduction[11,12] and is comparable to angiotensin-converting enzyme (ACE) inhibitors,[13] β blockers,[14] and hydrochlorothiazide.[10] Of note, when transdermal clonidine was compared with the β blocker atenolol—relative to acute exercise performance and the conditioning response—it substantially improved conditioning in young, otherwise healthy subjects with mild hypertension.[15]

Transdermal clonidine has been successfully employed as adjunctive therapy with drug classes such as ACE inhibitors[16] and calcium channel blockers[17]; however, when transdermal clonidine is provided as adjunctive therapy, it is unclear as to whether transdermal clonidine alone might have been sufficient for BP control.[16] Transdermal clonidine has also been shown to effectively reduce BP in hypertensive patients with type 2 diabetes while at the same time decreasing insulin resistance, microalbuminuria, and plasma fibrinogen.[18] In addition, clonidine (transdermal or oral) does not affect the cortisol response or the magnitude or rate of glucose recovery from insulin-induced hypoglycemia.[19]

Transdermal clonidine has also been effective in hemodialysis patients[20,21] and is particularly useful when such patients are otherwise noncompliant with their antihypertensive treatment regimen.[20] The dermal passage of clonidine from transdermal delivery systems appears not to be a particular problem in the renal failure patient notwithstanding histopathologic skin changes that are manifestations of the duration and severity of renal failure.[22]

ALTERNATIVE USES

In addition to its recognized use in the treatment of hypertension, transdermal clonidine has been used in select patients to assist in smoking cessation,[23] posttraumatic stress disorder, menopausal hot flashes,[24] and alcohol and opiate withdrawal syndromes, and to control postoperative sympathetic responses.[25] Transdermal clonidine does not, however, change headache frequency, pain intensity, or attack duration when used prophylactically in patients with episodic cluster headaches.[26] Of note, treatment with transdermal clonidine (compared with oral clonidine) has not routinely generated better results for these alternative uses, although clonidine delivered by this means tends to be better tolerated than oral clonidine.

A review of trials with clonidine found that it can lead to a small increase in the number of people likely to discontinue smoking; however, the quality of these trials is poor, which makes this evidence less reliable.[27,28] A treatment paradigm

Table. Average Plasma Clonidine Concentrations (pg/mL)* With a Transdermal Delivery System at Three Different Body Sites After 1 and 6 Days (N=12)

Site of Transdermal Patch	Day 1	Day 6
Chest	295	650
Upper outer arm	290	520
Upper outer thigh	95	360

*The therapeutic concentration of clonidine is typically in the 1000–2000 pg/mL range. Adapted from *Mild Hypertension.* Darmstadt, Germany: Steinkopf Verlag; 1984:143.[7]

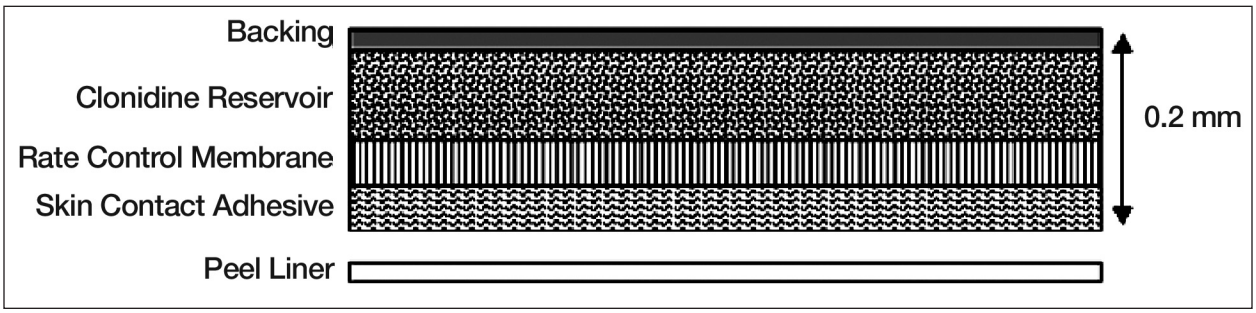

Figure. Schematic of a transdermal clonidine patch

with transdermal clonidine (typically with some oral clonidine as well) blunts surgically induced increases in sympathetic nervous system activity during the postoperative period and may be useful in preventing catecholamine-mediated adverse events in critically ill patients. Of note, clonidine sympatholytic activity primarily affects tonic activity and not the reactivity of the sympathetic nervous system, which is a useful pharmacologic attribute in the perioperative setting.[27]

DERMATOLOGIC REACTIONS

There is a relationship between the duration of clonidine patch use and the rate of development of allergic dermatitis; thus, skin irritation rates may be underestimated when such rates are drawn from short-term studies.[29–31] In a single-blind study with a 2-week placebo patch run-in and a 12-week maintenance period, the rates of erythema and induration were 52% vs. 11% and 24% vs. 0% for active drug vs. placebo, respectively.[32] The majority of these reactions were mild and subjects elected to continue with transdermal clonidine. Severe or generalized skin reactions were not encountered. In another series, 25% of patients discontinued treatment due to intolerable skin irritation.[10]

Skin reactions to transdermal clonidine can include subjective symptoms of pruritus and objective findings such as erythema, scaling, vesiculation, excoriation, and induration.[33] Hyperpigmentation, depigmentation, and pseudolymphoma can also occur.[34] Allergic dermatitis occurs more commonly in whites than in blacks[35] and in women than in men.[36] One report observed that the sensitization rate with transdermal clonidine was 34% and 18% in white women and men, respectively, and 14% and 8% in black women and men, respectively.[37] Depigmentation and hyperpigmentation have been observed in African Americans and may be irreversible in some patients.[38]

Potential causes of the allergic contact dermatitis could be the active drug, adhesive, diffusion membrane, solvent, or enhancer. Most studies have indicated that the skin reactions are related to the active drug itself and not other factors.[30,39,40] Systemic and/or skin reactions occur in a small number (1%–2%) of topically sensitized patients subsequently challenged with oral or IV clonidine.[30,39,41,42]

Treatment with hydrocortisone cream or over-the-counter antacids (magnesium–aluminum hydroxide suspension) has been used in an attempt to ameliorate skin reactions.[43,44] Hydrocortisone cream in a 0.5% concentration, whether applied under or around the edges of the patch, has occasionally been effective in preventing (or lessening) the contact dermatitis; however, this has been poorly studied other than for the observation that pretreatment of the skin with hydrocortisone increases clonidine absorption and thereby plasma levels. The variable response to hydrocortisone may reflect the relative weakness of this compound as a corticosteroid. Alternatively, an aerosolized spray of the more potent corticosteroid beclomethasone seems to favorably impact the skin sensitization seen with transdermal clonidine.[45] The drying effect of the steroid spray does not affect the adhesion of the patch to the skin surface, which has been viewed as a drawback with hydrocortisone cream.[45]

OTHER PATCH-SPECIFIC SIDE EFFECTS

Clonidine patches contain a significant reservoir of drug (2.5, 5.0, or 7.5 mg of clonidine, depending on the patch chosen). Clonidine patches can be licked, chewed, and/or swallowed, and in that event a large amount of clonidine can become available for systemic absorption. When ingested in this manner, psychoactive effects of clonidine such as a high, calming, or energizing effect occur.[46,47] The consequence of such ingestions can be particularly telling in young children, where the rather exquisite sensitivity to clonidine can result in significant bradycardia, central nervous system depression, and hypotension.[48]

PRACTICAL CONSIDERATIONS IN TRANSDERMAL CLONIDINE USE

Clonidine patches are available containing 2.5, 5.0, or 7.5 mg clonidine, which are designed to deliver

0.1, 0.2, or 0.3 mg/d of clonidine for 7 days, respectively. The patch is best placed on the upper arm or torso and rotated as to the site of application.[7] An unambiguous correlation between previous oral clonidine dose and the dose of transdermal clonidine required for an equivalent antihypertensive effect has not been established; thus, close observation of BP is advisable for at least 1 week following substitution of transdermal for oral clonidine. This is especially so in patients with severe hypertension, since rebound hypertension has been described while attempting to substitute transdermal for oral clonidine in a patient with severe hypertension.[49]

The transdermal route of administration for clonidine can be particularly useful in patients who are unable to receive orally administered antihypertensive medications.[50] Unlike oral clonidine, the transdermal form of clonidine has been infrequently associated with rebound hypertension.[9] This probably relates to an autotapering feature attributable to residual drug found in the skin where the removed patch had been previously affixed. Alternatively, the drug left behind in the skin following patch removal might prove problematic when rapid cessation of antihypertensive therapy is desired.

There is a 2–3 day delay in the onset of action after initial patch application. This slow onset is attributable to the formation of an epidermal clonidine reservoir beneath the patch as the drug binds to skin proteins. Use of the product is therefore not appropriate for the acute management of hypertensive urgencies; it would also not be effective when acutely administered during the perioperative period. This slow onset of action should also be kept in mind when transdermal clonidine replaces other antihypertensive therapy. In patients with more severe forms of hypertension, the prior antihypertensive therapy may have to be continued (in full or in part) until sufficient clonidine has been delivered transdermally to influence BP.

ECONOMICS

In a rational marketplace, one might expect a higher-priced product, such as transdermal clonidine, to prevail if it could be shown to offer both clinical benefits as well as savings in overall care costs. This has not, however, been the case for this formulation of clonidine. The considerably higher cost of transdermal clonidine has proven a disincentive to its more widespread use. There is a clear need for proof that delivery systems-based variations of established pharmaceuticals provide legitimate value.[51]

CONCLUSIONS

Clonidine, a central α-adrenergic agonist, is a safe and efficacious antihypertensive agent that produces minimal adverse metabolic effects. It is an effective therapy for the treatment of diverse forms of hypertension irrespective of age, gender, or ethnicity. In its oral form, clonidine is often associated with side effects of excessive drowsiness and/or dry mouth. The transdermal delivery system has a substantially lower incidence of these side effects, and it provides a week of therapy with a single administration. The latter feature avoids the sometimes hectic peak-valley effects seen with oral clonidine, particularly when it is being given once or twice daily. The therapeutic advantages of transdermal clonidine have to be weighed against a moderately high incidence of skin reactions as well as a much higher monthly cost compared with orally administered clonidine.

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