PROPANTHELINE BROMIDE IN THE MANAGEMENT OF HYPERHIDROSIS ASSOCIATED WITH SPINAL CORD INJURY

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OBJECTIVE: To report 2 cases in which oral propantheline reduced the discomfort associated with sweating related to spinal cord injury (SCI), and to review the literature on the management of SCI-related sweating.

CASE SUMMARIES: Case 1: A 27-year-old quadriplegic man with an American Spinal Injury Association (ASIA) Frankel class C injury to C5/C6 experienced profuse sweating and requested propantheline. He stated that he had received the medication previously and reported that propantheline 15 mg tid had controlled his sweating. Propantheline bromide was reinstituted, and within 24 hours, the patient's episodes of profuse sweating had decreased markedly in number and frequency. Case 2: A 35-year-old quadriplegic woman had an ASIA class D lesion at C3. Since her injury, she had experienced profuse sweating that worsened when she became cold and at night. She stated that her sweating was under control as long as she took propantheline. Propantheline therapy was continued and no further sweating episodes have occurred.

DATA SOURCE: A MEDLINE search was used to identify pertinent literature including reviews. Standard texts and texts referenced in the pertinent literature also were examined.

STUDY SELECTION: All available sources of information were reviewed.

DATA SYNTHESIS: The earliest case reports of systemic therapy for hyperhidrosis described the use of the anticholinergic methantheline bromide. Methantheline in combination with ergoloid mesylates also was suggested for the treatment of congenital hyperhidrosis. Local topical therapy for hyperhidrosis, such as aluminum chlorohydrate and aluminum chloride, the active ingredients in some antiperspirants, have been tried with some success. Talc, starch, and other powders have been suggested to absorb excessive sweat. Formalin and glutaraldehyde also have been used. Topical propantheline bromide has been used successfully in treating palmar and plantar hidrosis. Clonazepam has been used successfully in a case of unilateral localized hyperhidrosis. Systemic phenoxybenzamine has been used with some success and there have been attempts at other systemic therapy using mecamylamine, atropine, propoxyphenel, and methenamine. Scopolamine patches also have been used successfully in a small number of patients. Other agents that have been used include dibenamine, piperoxan, and phentolamine. Systemic propantheline also has been listed as an agent with potential efficacy in treating the profuse sweating associated with SCI, but was not recommended primarily because of adverse effects and difficulty in titrating to the lowest effective dosage. However, studies or case reports specific to the use of propantheline in patients with SCI appear to be lacking, as are reports of direct comparison between propantheline and other agents.

DISCUSSION: Concerning the mechanism of action of propantheline bromide for hyperhidrosis, it seems reasonable to attribute its effects to the drug's well-documented anticholinergic/antimuscarinic actions. At dosages used to effectively treat neurogenic bladder, propantheline bromide also should block the muscarinic receptors responsible for sweat gland stimulation. Central nervous system adverse effects should be minimal at usual clinical dosages, as propantheline does not cross the blood–brain barrier.

CONCLUSIONS: It would appear that in some patients with SCI who are subject to incidental episodes of profuse sweating, oral propantheline may offer some relief and may, in fact, be well tolerated, as in the cases described. Additionally, propantheline would seem a good therapeutic choice in SCI patients with excessive sweating and neurogenic bladder dysfunction who may derive dual benefit from the agent.

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MANY PATIENTS with spinal cord injury (SCI) experience hyperhidrosis. Thirty-six percent (56 of 154) of the patients responding in 1 study reported current problems with sweating and another 7% (11 of 154) had problems in the past.[1] In a total of 14.6% (28 of 192) of respondents who reported annoying hyperhidrosis, no contributing cause could be found.[1]

CASE REPORTS

The following cases describe a pharmacotherapeutic intervention that provided 2 patients with some relief, and in a small way improved the patients' quality of life.

CASE 1

In 1982, a 27-year-old quadriplegic man was readmitted to the hospital with an infection of the urinary tract and possible pyelonephritis. He had sustained an American Spinal Injury Association (ASIA) Frankel class C injury to C5/C6 when he fell from a tree at age 17 years. During the course of his hospitalization, he experienced profuse sweating. In reporting this to the patient care team, the patient requested propantheline. He stated that, prior to this admission, he had received the medication at a rehabilitation center. The original indication for the propantheline was unclear, but was probably used to manage the patient's voiding dysfunction (neurogenic bladder dysfunction). The patient reported that propantheline 15 mg tid had incidentally controlled his sweating episodes.

Propantheline bromide was reinstituted, and within 24 hours, the patient's episodes of profuse sweating had decreased markedly in number and frequency. Although not completely resolved, the condition was clearly less annoying for the patient.

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CASE 2

In 1993, a 35-year-old HIV-positive woman was admitted to the hospital because of a fever, anemia, and worsening of her decubitus ulcers. She was quadriplegic as a result of a gunshot wound to the back 17 years earlier, resulting in an ASIA class D lesion at C3. She had a neurogenic bladder and used an indwelling Foley catheter. Medications on admission were methadone 10 mg tid, zidovudine 100 mg tid, diazepam 10 mg tid, and propantheline 15 mg tid.

Empiric therapy was initiated with ticarcillin/clavulanate and gentamicin. The patient was placed on respiratory isolation until the result of the cultures could be obtained. Following debridement of her decubitus ulcers, her temperature returned to normal and her antibiotic therapy was changed to oral ciprofloxacin. Since her injury, she had experienced profuse sweating, worsening when she became cold and at night. She stated that her sweating was under control as long as she took propantheline. The propantheline was continued and no further sweating episodes have occurred.

Hyperhidrosis

Hyperhidrosis is a term that is applied to any condition in which an inappropriately large amount of sweat is produced.[2] Profuse sweating in patients who have spinal cord lesions was described first in 1917.[3] Although hyperhidrosis is associated commonly with damage to the cervicalthoracic sympathetic ganglia or disturbances in the autonomic nervous system, its etiology in SCI is not completely understood.[2,4] It is known that the sympathetic eccrine sweat glands also are cholinergically innervated,[4,5] and when the connection between the cerebrum and spinal cord is disrupted, sweat reflexes below the level of the injury are abolished.[5] However, when the spinal reflexes return, the sweat glands may become hyperreactive to afferent stimulation.[5]

Sweating in Spinal Cord Injury

It appears that there are at least 2 types of sweating noted in SCI: autonomic hyperreflexia or dysreflexia, secondary to various, generally noxious, stimuli[6] (e.g., bowel or bladder distention) and associated with other serious autonomic phenomena; and incidental sweating, not associated with other autonomic phenomena and often related to simple factors such as ambient temperature. Early study in patients with SCI suggested that if there was injury above C8, no sweating response to ambient temperatures was possible,[6] and that with injury above T9 or T10, heat-induced sweating did not occur below the level of the lesion.[6] However, studies now suggest that patients with higher cervical cord lesions (C5–C6) do have a sweating response to increased temperatures.[7]

Autonomic Hyperreflexia/Dysreflexia

Hyperreflexic sweating is an indication of unchecked spinal cord facilitation and can be precipitated by afferent stimuli from the bladder, rectum, and other sources. It has been described as a manifestation of mass reflex or autonomic crisis occurring particularly in patients with cervical or high thoracic lesions.[8] This type of sweating may be caused by local effects[2,6]: bowel or bladder distention,[4-6,9] impulses transmitted into the isolated cord segment,[4,6] or conditions that would otherwise elicit pain.[10] Other circumstances reported to precipitate hyperreflexic sweating below the lesion include muscle spasm, catheterization, postural changes, and bladder infection.[9] These noxious stimuli initiate the afferent impulses, which enter the spinal cord and lead to sympathetic responses.

Although sweating is commonly associated with autonomic hyperreflexia, the more severe sequelae deserve comment. Autonomic hyperreflexia is characterized by sudden onset of headache and hypertension in a patient with SCI. These exaggerated responses can include vasoconstriction leading to hypertension, piloerection, bradycardia, and flushing above the lesion, in addition to sweating. Because autonomic hyperreflexia is potentially life-threatening, the blood pressure of an SCI patient reporting headache or sweating should be checked and significant increases should be treated by eliminating the causes (e.g., bladder distention) and with antihypertensive pharmacotherapy as appropriate.[11]

Incidental Sweating

Although not life-threatening, this form of hyperhidrosis can be an aggravation to the patient, resulting in discomfort and embarrassment and evoking reports to the clinician who often has little to offer the patient to provide relief. Typically, therapy is either unsuccessful or causes unacceptable adverse effects.[1]

It has long been known that sweat glands are under sympathetic control, but also respond to parasympathetic drugs. Haimovici demonstrated that secretory activity of sweat glands was stimulated by intradermal injection of cholinergic and adrenergic drugs (i.e., epinephrine, acetylcholine, methacholine).[12]

Pharmacotherapy of Sweating in Spinal Cord Injury

The earliest reports of systemic therapy for hyperhidrosis[13] described the use of the anticholinergic methantheline bromide in 4 women following the observation that patients being treated for gastrointestinal disorders with methantheline commented on the dryness of their hands.[14] Methantheline in combination with ergoloid mesylates also was suggested for the treatment of congenital hyperhidrosis.[15]

Local topical therapy for hyperhidrosis, such as aluminum chlorohydrate and aluminum chloride, the active ingredients in some antiperspirants, have been tried with some success.[2,16,17] Talc, starch, and other powders have been suggested to absorb excessive sweat.[17] Formalin and glutaraldehyde also have been used.[17] Topical propantheline bromide has been used successfully in treating palmar and plantar hidrosis.[16]

The aim of treatment of hyperhidrosis in patients with SCI commonly is to block the sympathetic or cholinergic activation of the sweat glands.[1] Clonazepam has been used successfully in a case of unilateral localized hyperhidrosis.[18] Systemic phenoxybenzamine has been used with some success,[19] and there have been attempts at other systemic therapy using mecamylamine,[4,20] atropine,[4,20] propoxyphene,[1,4] and methenamine.[21] Scopolamine patches also have been used successfully in a small number of patients.[22] Other agents that have been used include dibenamine (an alpha-adrenergic antagonist no longer used in humans), piperoxan, and phentolamine.[15]

Systemic propantheline, an agent structurally related to methantheline, also has been listed as an agent with potential efficacy in treating the profuse sweating associated with SCI,[4,17,20] but was not recommended primarily because of adverse effects and difficulty in titrating to the lowest effective dose. However, reports specific to the use of propantheline in patients with SCI appear to be lacking, as are reports of a direct comparison between propantheline and other agents.

Discussion

Concerning the mechanism of action of propantheline bromide for hyperhidrosis, it seems reasonable to attribute its effects to the drug's well-documented anticholinergic/antimuscarinic actions. It is known that topically applied propantheline bromide appears to exert its action by inhibiting the muscarinic receptors locally.[22] Antimuscarinics competitively inhibit the action of acetylcholine at the postganglionic cholinergic innervations. They also inhibit its action on smooth muscles, secretory glands, and central nervous system sites, as well as various physiologic secretory functions. These include secretions from the bronchioles and salivary and sweat glands. The inhibition at these sites is dose-dependent, with the most sensitive being the salivary, bronchial, and sweat glands. Less sensitive are pupillary dilation, ocular accommodation, and heart rate. Even less sensitive are the detrusor muscles of the bladder and the smooth muscle of the gastrointestinal tract, with gastric secretion and motility being the least sensitive. Thus, at dosages used to treat neurogenic bladder effectively, propantheline bromide also should block the muscarinic receptors responsible for sweat gland stimulation.[23] Central nervous system adverse effects should be minimal at normal clinical dosages, as propantheline does not cross the blood–brain barrier.

Summary

It would appear that in some patients with SCI who are subject to incidental episodes of profuse sweating, oral propantheline may offer some relief and may, in fact, be well tolerated, as in the cases described. Additionally, propantheline would seem a good therapeutic choice in SCI patients with excessive sweating and neurogenic bladder dysfunction who may derive dual benefit from the agent.

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EXTRACTO

OBJETIVO: Informar sobre 2 casos en los cuales el uso oral de propantelina oral redujo las molestias asociadas con la sudoración que se produce en pacientes con lesiones del cordón espinal, y revisar la literatura en cuanto al manejo de este síntoma.

RESUMEN DE CASOS: Caso 1: Un hombre cuadriplégico de 27 años con una lesión Frankel Clase C de las cervicales 5 y 6 según la Asociación Americana de Lesión Espinal (AALE) se quejaba de sudoración profusa y solicitó se le administrara propantelina. Indicó que lo había utilizado previamente en dosis de 15 mg 3 veces al día logrando control de la sudoración. Se le administró nuevamente el bromuro de propantelina y, en 24 horas, los episodios de sudoración profusa disminuyeron marcadamente. Caso 2: Una mujer cuadriplégica de 35 años con lesión de la cervical 3 Clase D según la AALE se quejaba de sudoración abundante, que empeoraba con el fría durante la noche. Durante el tratamiento con propantelina no tuvo episodios de sudoración.

FUENTES DE INFORMACIÓN: Una búsqueda bibliográfica en MEDLINE fue realizada para identificar literatura pertinente incluyendo artículos de revisión. Libros de texto también fueron revisados.

SELECCIÓN DE FUENTES DE INFORMACIÓN: Todas las fuentes de información disponibles fueron revisadas.

SÍNTESIS: Los primeros informes donde se utilizó terapia sistémica para el manejo de hiperhidrosis describen el uso del anticolinérgico bromuro de metantelina. La combinación de metantelina con mesilatos ergoloides ha sido sugerido para el tratamiento de hiperhidrosis congénita. Terapia

tópica para la hiperhidrosis, como el clorhidrato de aluminio y cloruro de aluminio, ambos ingredientes activos de los antiperspirantes han sido utilizado en el pasado con algún éxito. Talco, almidón, y otros polvos se han sugerido para absorber el sudor excesivo. También se han utilizado formalina y glutaraldehido. Bromuro de propantelina tópico ha sido utilizado exitosamente para tratar hidrosis de la palma de la mano y de la planta del pie. Clonazepam se ha utilizado con éxito en un caso de hiperhidrosis unilateral localizada. Fenoxibenzamina sistémica se ha usado con algún éxito y también se ha intentado el uso sistémico de mecamilamina, clorhidrato de dextropropoxifeno, y metenamina. Parches de escopolamina han dado buenos resultados en algunos pacientes. Otros agentes utilizados incluyen dibenamina, piperoxán (benzodióxano), y fentolamina. El uso sistémico de propantelina se ha mencionado entre los medicamentos que pueden ser efectivos en el tratamiento de sudoración profusa asociada a lesiones del cordón espinal, pero en el pasado no se recomendaba por sus efectos secundarios y la dificultad para establecer la dosis mínima efectiva. Sin embargo, los estudios o informes de casos sobre el uso de propantelina en pacientes con lesiones del cordón espinal son escasos al igual que los estudios comparativos de propantelina con otros agentes.

DISCUSIÓN: Al especular en cuanto al mecanismo de acción de bromuro de propantelina en el tratamiento de hiperhidrosis, se pueden atribuir sus efectos a la acción anticolinérgica/antimuscarínica. En dosis utilizadas para tratar vejiga neurogénica, bromuro de propantelina debe bloquear los receptores muscarínicos responsables de la estimulación de las glándulas de la sudoración. Los efectos secundarios al sistema nervioso central deben ser mínimos en dosis usuales, ya que propantelina no cruza la barrera cerebral.

CONCLUSIÓNES: En algunos pacientes con lesiones del cordón espinal que padecen de episodios de sudoración profusa, propantelina oral puede ofrecer algún grado de alivio y ser bien tolerado como en los casos aquí descritos. En adición propantelina aparenta ser una buena alternativa terapéutica en pacientes con lesiones del cordón espinal que sufren de sudoración excesiva y de disfunción de vejiga neurogénica.

RAFAELA MENA

RÉSUMÉ

OBJECTIF: Rapporter 2 cas de patients chez qui l'administration de propanthéline par voie orale a permis de diminuer l'inconfort associé à la sudation secondaire à une lésion de la moelle épinière (LMÉ). Réviser la littérature scientifique sur le traitement de la sudation secondaire à une LMÉ.

RÉSUMÉ DES CAS: Cas 1: Un homme de 27 ans, quadraplégique, ayant subi une LMÉ au niveau des vertèbres C5-C6, se plaignait de sudation profuse, problème pour lequel il demandait la propanthéline. L'utilisation antérieure de la propanthéline à une dose de 15 mg 3 fois par jour avait contrôlé la sudation. Moins de 24 heures après avoir débuté le traitement à la propanthéline, une diminution importante du nombre et de la fréquence des épisodes de sudation profuse était notée. Cas 2: Une femme de 35 ans, quadraplégique, ayant subi une LMÉ au niveau de C3, se plaignait de sudation profuse s'aggravant lorsqu'elle prenait froid et la nuit. Depuis qu'elle prend de la propanthéline, elle rapporte que ses symptômes sont sous contrôle.

REVUE DE LA LITTÉRATURE: Une recherche a été effectuée sur MEDLINE afin d'identifier la littérature pertinente sur le sujet. Toutes les sources d'information disponibles ont été considérées.

RÉSUMÉ: Les premiers articles décrivant le traitement systémique de l'hyperhydrose font mention d'un agent anticholinergique, le bromure de méthanthéline. L'utilisation de la méthanthéline en association avec le mésylate d'ergoloïdes était également suggérée dans le traitement de l'hyperhydrose congénitale. Le traitement topique à base de chlorhydrate d'aluminium ou de chlorure d'aluminium, ingrédients actifs de plusieurs antisudorifiques, s'est avéré efficace chez certains patients. L'emploi de talc, d'amidon ainsi que d'autres poudres a été suggéré afin d'absorber l'excès de sueur. La formaline et la glutaraldéhyde ont aussi été utilisées. L'application topique de bromure de propanthéline s'est aussi révélée efficace dans le traitement de l'hyperhydrose palmaire et plantaire. Plusieurs autres médicaments se sont avérés utiles dans le traitement de l'hyperhydrose: clonazépam, phénoxybenzamine, mécamylamine, atropine, dextropropoxyphène, méthénamine, scopolamine transdermique, dibenamine, piperoxan et phentolamine. La propanthéline systémique a aussi été identifiée comme traitement potentiel de la sudation profuse associée à une LMÉ. Cependant, elle n'était pas recommandée en raison de ses effets secondaires et de la difficulté à déterminer la dose minimale efficace. Aucon rapport ou étude sur l'utilisation spécifique de la propanthéline chez les patients souffrant d'une LMÉ n'avait été publié jusqu'à présent.

DISCUSSION: L'activité du bromure de propanthéline dans le traitement de l'hyperhydrose peut être attribuée à ses propriétés anticholinergiques-antimuscariniques. Aux doses utilisées dans le traitement de la vessie neurogène, la propanthéline devrait aussi bloquer les récepteurs muscariniques responsables de la stimulation des glandes sudoripares. Les effets indésirables centraux devraient être peu importants aux doses usuelles puisque la propanthéline ne traverse pas la barrière hémato-encéphalique.

CONCLUSIONS: Il semble que l'utilisation de propanthéline par voie orale puisse s'avérer efficace dans le traitement de la sudation profuse chez les malades souffrant d'une LMÉ. De plus, le traitement à la propanthéline pourrait être un choix intéressant chez les malades ayant subi une LMÉ et souffrant à la fois de sudation excessive et d'un problème de vessie neurogène.

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