Scopolamine and the Murder of King Hamlet

Basilio Aristidis Kotsias, MD, PhD

The events narrated by Shakespeare in his tragedy *Hamlet* are the following: King Hamlet of Denmark dies suddenly and his brother Claudius a few weeks later marries the widow, his sister-in-law, Queen Gertrude; according to the official explanation, a snake-bite was the cause of his death. The ghost of the king appears before his son, Prince Hamlet, and tells him that his own brother, now his converted stepfather, has killed him, pouring into his ear the contents of an ampoule of henbane (Act I, scene 5). I cite the ghost’s account in full:

Sleeping within mine orchard,
My custom always in the afternoon,
Upon my secure hour thy uncle stole,
With juice of cursed hebona [henbane] in a vial,
And in the porches of mine ears did pour
The leperous distilment; whose effect
Holds such as enmity with blood of man
That swift as quicksilver it courses through
The natural gates and alleys of the body,
And with a sudden vigour it doth posset
And curd, like eager droppings into milk,
The thin and wholesome blood: so dit it mine:
And a most instant tetter bark’d about,
Most lazar-like, with vile and loathsome crust,
All my smooth body.

In this article I attempt to analyze and discuss in the light of present medical information this scene of *Hamlet*. How did Shakespeare come to this singular idea? Could the venom extracted from a narcotic plant with beautiful leaves, a foul odor, yellow flowers above and purple below, have been responsible for the death of King Hamlet? If it is accepted that the extracted henbane was of good quality, could the manner chosen by the fratricide have been effective? I conclude that it was possible to accomplish the murder as it was written in the tragedy.

Incidentally, we recall that although this subject in *Hamlet* had received attention in the past,2-6 it has an additional interest because the ghost in Shakespeare’s play speaks of the rapidity of the toxic effect and at the same time describes what may be considered the blood circulation. Readers may be interested to know that, although Shakespeare and Harvey were contemporaries, *Hamlet* was published in 1603, 25 years before *The Motu Cordis*.

Henbane or hebona is extracted from the seeds and leaves of *Hyoscyamus niger* and *Scopolia carniolica*, plants belonging to the Solanaceae family that also includes common foods such as tomatoes, potatoes, eggplant, peppers, and tobacco. *Hyoscyamus* and *Scopolia* contain the active ingredients scopolamine (or hyoscyamine)7,8 whereas atropine is extracted from other plants of the same family. All these substances have no known function in the plants in which they are found.

Scopolamine and atropine are anticholinergic drugs that block the acetylcholine muscarinic receptors in a competitive and nonspecific manner, preventing a close interaction between the ligand and lipophilic sites on the receptor.7,8,10 Muscarinic receptors are G protein–coupled receptors and mediate their inhibitory or excitatory responses by activating a cascade of intracellular pathways rather than the direct opening of an ion channel as with nicotinic receptors. Molecular cloning techniques identified 5 different subtypes of muscarinic receptors that share common features, including specificity of binding for the agonists and the classic antagonists. M1,
M2, and M3 receptors are associated with an increase in the production of inositol triphosphate, while M2 and M4 subtypes decrease the levels of cyclic adenosine monophosphate by inhibiting adenosine cyclase. The tissue distribution differs for each subtype. M1 receptors are found in the forebrain, especially in the hippocampus and cerebral cortex. M2 receptors are found in the heart and brainstem, while M3 receptors are found in smooth muscle, exocrine glands, and the cerebral cortex. M4 receptors are found in the neostriatum and M4 receptor mRNA is found in the substantia nigra.

The absorption of scopolamine through the skin is limited, although a preparation in the form of transdermal patches placed over the mastoid region of the neck is used for the prevention of motion sickness. The relative ease with which scopolamine crosses the blood-brain barrier makes its effects on the central nervous system more important than other anticholinergic drugs. For this reason, it is used not only in the inhibition of parasymptomatic function, but also in experimental studies involving memory. The half-life of scopolamine in plasma is 3 hours and its use in toxic doses (about 10 mg) is accompanied by a rapid and weak pulse, paralysis of the iris, blurred vision, dry, warm, and reddish skin, decreased intestinal peristalsis and motility, ataxia, hallucinations, and eventually coma and death.

Both atropine and scopolamine have a long history involving witchcraft and the analgesic and anaesthetic actions of these drugs, isolated or in combination with opioids and stramonium, have been known for centuries and related by Dioscorides in the first century BC, Cervantes (Don Quixote, part I, chapter 18), and Calderón de la Barca (La Vida Es Sueño, second episode). For centuries, the Roman spongia somnifera, remembered today for the association it had with the punishment of crucifixion, was used as vector of several types of drugs, including henbane among others.

Shakespeare may well have been influenced by contemporary events or other authors choosing this finesse in the administration of a “mixture rank, of midnight weeds collected.” In 1560, the surgeon A. Pare was accused of having poisoned Francis II, King of France, by blowing venous powders into his ear (a white powder was found in one of his caps). In 1538, Francisco Maria I, Duke of Urbino, was murdered in Pésaro. The crime was attributed to some Luigi Gonzaga, who might have bribed the barber and surgeon of the noble to introduce the venom into his ear. It is possible that Shakespeare was aware of these episodes and used the last one in the scene of the play within the play (Act III, scene 2). The actors perform “The Murder of Gonzago” in which the name of the murderer is exchanged for that of the victim, slightly altered, whereas a murderer in Marlowe’s play Edward II (Act V, scene 4) uses poisonous powders introduced into the ear with the help of a feather.

The skin lining the ear canal is rigidly adhered to the underlying bone and cartilage and is very vulnerable to mechanical damage, such as a scratch; it can become inflamed and the vasodilation or neovascularization provoked by the inflammation makes it more capable of absorbing drugs. The poorly vascularized tympanic membrane is covered by skin similar to that of the external auditory canal; however, it is reduced to a fine layer of epidermis and is less fit for rapid drug absorption. The possibility of a murder via auris was known to occur in 16th-century Italy, and it was based on the knowledge of that time about the direct absorption of some substances from the ear. Pliny in his Natural History (Book 25.4.17), published in English in 1601, recommended pouring oil of henbane into the ears for use in earache, though he warns that it may cause mental disorder. Henbane was an official drug mentioned in old English pharmacopoeias and dispensatories and it was used as well as the cannabis extract in the form of eardrops in the treatment of earache. Many years ago, Macht demonstrated with experiments in animals that certain poisons, including scopolamine, can be absorbed through the intact ear and often likewise skin eruptions and shorten the coagulation time of blood.

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autonomic functions or a tachycardiac effect on a diseased heart. Finally, there exists the possibility that everything related to the apparition of the ghost on the platform before the castle of Elsinore was a product of Shakespeare's fantasy, as well as the death of the melancholic prince, wounded by the poisoned sword (with what venom?) that Laertes held. If this were true, our interpretation would result in pure fiction.

Accepted for publication November 30, 2001.
I thank Susie Kestner, J. A. Barcat, L. O. Aiello, and both reviewers for their valuable help with the manuscript.

Corresponding author and reprints: Basilio Aristidis Kotsias, MD, PhD, Instituto de Investigaciones Medicas A. Lanari, University of Buenos Aires, C. de Malvinas 3150, 1427 Buenos Aires-Argentina (e-mail: kotsias@yahoo.com).

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