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The pharmacology of medieval sedatives: The "Great Rest" of the *Antidotarium Nicolai*

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ABSTRACT

Ethnopharmacological relevance: Past practices of compound drugs from different plant ingredients enjoyed remarkable longevity over centuries yet are largely dismissed by modern science as subtherapeutic, lethal or fanciful.
Aim of the study: To examine the phytochemical content of a popular medieval opiate drug called the "Great Rest" and gauge the bioavailability and combined effects of its alkaloid compounds (morphine, codeine, hyoscyamine, scopolamine) on the human body according to modern pharmacokinetic and pharmacodynamic parameters established for these compounds.
Calculations and theory: We reviewed the most recent studies on the pharmacodynamics of morphine, codeine, hyoscyamine and scopolamine to ascertain plasma concentrations required for different physiological effects and applied these findings to dosage of the *Great Rest*.
Results: Given the proportional quantities of the alkaloid rich plants, we calculate the optimal dose of *Great Rest* to be 3.1 ± 0.1–5.3 ± 0.76 g and reveal that the lethal dose of *Great Rest* is double the therapeutic concentration where all three alkaloid compounds are biologically active.
Conclusion: This study helps establish the effective dose (ED_{50}), toxic dose (TD_{50}) and lethal dose (LD_{50}) rates for the ingestion of raw opium, henbane and mandrake, and describes their probable combined effects, which may be applied to similar types of pre-modern pharmaceuticals to reveal the empirical logic behind past practices.

1. Introduction

The compound medicines of the ancient, medieval and early modern world are a historical embarrassment which science and modernity would rather forget. Pharmaceutical concoctions containing anything from a half-dozen to over sixty ingredients were carefully copied out by scribes, and then painstakingly arranged by typesetters, to transmit information about drugs that were famous across Europe for hundreds of years. Such drugs have often been dismissed by modern science as sub-therapeutic, lethal, or simply placebos (Shapiro and Shapiro, 2000; Sneader, 2005; Raviña, 2011). A re-examination of the ingredients of these drugs, in light of modern research on phytochemistry, biochemistry and pharmacology provides better perspectives for understanding their popularity. This type of research may take many angles, such as investigating the nutritional and prophylactic role of the ingredients of some drugs (for vitamins, antioxidants, anti-inflammatory effects: Norton (2006)), the anthelmintic and carminative properties of drugs for gastrointestinal problems (Ali et al., 2008; Haniadka et al., 2013), plants with hypoglycemic properties to treat diabetes (Riddle, 2004: Helmstädter, 2007; Patel et al., 2012), antimicrobial properties of plants in wound-healing recipes (Watkins et al., 2012), and the synergistic and/or adjuvant effects of compounds from different plants combined (Williamson, 2001; Dev, 2012; Yang et al., 2014).

In this study, we examine the dosage level of the alkaloid-rich plants of opium, henbane and mandrake in one popular medieval drug known as the "Great Rest" (*Requies magna*) to determine its probable physiological effect on the human body. These three plants were frequently combined in pre-modern drugs intended for sedation and/or analgesia, yet their dosage levels and combined effects have not been sufficiently considered with a view to what we now know about the phytochemistry of these plants and the pharmacology of their active compounds. To remedy this deficit, and to provide a point of departure for future inquiry, we chose to analyze the *Great Rest* for three reasons:

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Authority and influence. The *Great Rest* appears in an incredibly influential formulary book compiled in twelfth-century Salerno, the *Antidotary of Nicholas* (*Antidotarium Nicolai*) which was largely considered the Bible of compound pharmacy in the Middle Ages, its use is mandatory in some medieval states (Goltz, 1976; Roberg, 2002, 2007a, 2007b, 2011). It was translated into European vernacular languages and printed in the Renaissance period and beyond (Fontanella, 2000; Carrillo Linares, 2005).

Precise dosage. A major source of the *Antidotary* authority and popularity was owed in part to its precise measurements of ingredients and dosages for every drug (electuaries, unguents, pills, syrups, plasters etc.: Goltz, 1976, 58–59; Schmitz, 1998; Bergmann 2003, 2008). The recipe for the *Great Rest* expresses unusual concern about its potency and advises about its intermittent or partial administration. The empirical knowledge behind these comments is also reflected, we suggest, in the amounts of the three plants in the recipe and the stipulated dosage of the compounded drug.

The plant alkaloids. The single therapeutic purpose of the *Great Rest* was to provide sedation and/or analgesia, using combination of opium, henbane and mandrake that is common to many medieval and pre-modern opiates and sedatives. Modern medical use and pharmacological study of the principal active alkaloid compounds in these plants—morphine and codeine from opium, hyoscyamine and scopolamine from henbane and mandrake—and their effect on the central nervous system have established pharmacokinetic and pharmacodynamic parameters that can be applied to the ingestion of these compounds in crude form (Norn et al., 2005; Bahmanzadegan et al., 2009; Peduto, 2001).

2. The *Antidotarium Nicolai* and its *Great Rest*

We know nothing of Nicholas of Salerno's life or career, but he carefully calculated amounts of the ingredients according to existing Salernitan measurements (dram, scruple, grain: Bergmann (2003, 2008)) to ensure that the batch from the recipe never exceeds one or two pounds, a practical amount for practicing pharmacists who were becoming publicly recognized professionals at this time (Sappert and von Wolfgang-Hagen, 1957; Sonnedeker, 1986; Bénézet, 1999: on Salerno, Paravicini Bagliani and Jacquart, 2008). In his prologue, Nicholas claimed to have written the *Antidotarium* "at the request of those who wished to learn the practice of medicine (*practica medicinae*)", but ended the prologue on a note of mercantile wisdom: "through this (proper knowledge of common ingredients) comes a simple and sure point about business: keep the price low, and the dispensing moderate." (*leve pretium et moderata dispensatio*: Latin text in Van den Berg, 1917, 5; and Goltz, 1976, Appendix).

The *Great Rest* is one of the several opiates that appear in the *Antidotarium Nicholai*, some of which contain similar amounts of opium to that found in the *Great Rest*, and likewise use henbane and mandrake. The *Great Rest*, however, differs in that after giving the recipe, Nicholas expresses some caution about the dose and administration of the drug, the only one he specifically names as an "opiate" (though he used the term in his epilogue), calling it "cold", a classification based on its "deadening" effect on the body, dating back to ancient Greek pharmacology (Everett, 2012). An English translation of the Latin text (Van den Berg, 1917, 131) follows: paragraphing and conversion to grams have been added (Table 1).

> ***Great rest or Great medicine***. *It is called rest because it offers rest to patients, and it offers periodic sleep especially to those suffering daily, tertian, quartan, and very acute fevers.*[2] *Six parts are made from one pound. Take three drams* (10.244 g) *each of roses and violets; one dram and a half* (5.8 g) *each of opium, henbane, meconium of white (opium) poppy, mandrake, wild lettuce, seeds of purslane, fleawort, nutmeg, cinnamon, and sugar. Two scruples and five grains* (2.9 g) *of white and red and citric sandalwood, ash, and tragacanth. Give with violet syrup to patients suffering acute fever; we can give it to them intermittently mixed with honey. It is given to those suffering quartan fevers with warm wine when the fever is acute or severe, and to these suffering tertian fever with warm water or syrup.*
>
> *The Rest is an opiate that is cold. It is especially good for inducing sleep when an amount of the size of a chestnut is given. However, when it is given to men who are almost healthy, they really must eat or dine in a regular manner. And afterwards, when it is given to someone going to sleep, it can be blended with rose juice or violet syrup if they are averse to taking it: but purify it before giving it. This will not have any effect whatsoever for it is still very powerful when given this way.*
>
> *It should also be added that from the different ingredients of this medicine a syrup is made that is very good for inducing sleep. And of course some ingredients they boil in water, crush, strain, and add sugar to make a syrup. This also can be given to those suffering from acute fevers for inducing sleep.*

Table 1
Ingredients of the *Great Rest* (*Requies magna*) to be administered in a mixture with violet syrup or honey (sugar).

Ingredient	Mass in Salernitan terms	Modern (g)
Roses	3 Dr (ams)	10.244
Violets	3 Dr	10.244
Opium	1.5 Dr	5.8
Henbane	1.5 Dr	5.8
Meconium of opium	1.5 Dr	5.8
Mandrake	1.5 Dr	5.8
Wild Lettuce	1.5 Dr	5.8
Seeds of Purslane	1.5 Dr	5.8
Nutmeg	1.5 Dr	5.8
Fleawort	1.5 Dr	5.8
Cinnamon	1.5 Dr	5.8
Sugar	1.5 Dr	5.8
White sandalwood	2 Scr(uples), 5 gra(ins)	2.9
Red Sandalwood	2 Scr, 5 gra	2.9
Citric Sandalwood	2 Scr, 5 gra	2.9
Ash	2 Scr, 5 gra	2.9
Tragacanth	2 Scr, 5 gra	2.9
TOTAL	27.5 Dr, 25 gra, 10 scr	93.0

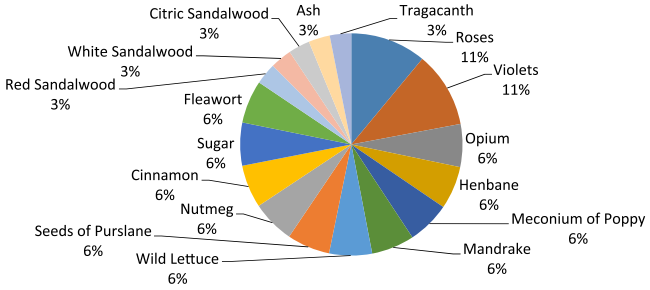

Fig. 1. Percent Composition of the *Great Rest* (*Requies magna*).

[2] These categories of fever, commonly used in Classical Antiquity and the Middle Ages, were inherited from Hippocratic writings, based on the periodicity of paroxisms: a 'tertian' fever peaked on the third day, and so on: see Nutton (2012), *(footnote continued)* Jouanna (2001). While some scholars have identified different diseases such as malaria for tertian and quartan fever (Garcia et al., 2001), the interminable interpretive problems of medieval descriptions and symptomology need not distract us here. The goal of the *Great Rest* was to provide relief from fevers in general by promoting sleep.

As Table 1 outlines, the *Great Rest* can be broken down and approximated to its modern mass counterpart. It is observed that the recipe yields roughly 93 modern grams; opium, henbane and mandrake make up 12.46%, 6.23% and 6.23% of the *Great Rest* respectively (Fig. 1).

3. Calculations and theory

We translated the *Great Rest* from the *Antidotarium Nicholai*, using Bergmann (2003, 2008) to translate the measurements used in twelfth-century Salerno to their modern value counterparts (Table 1). Since the instructions for the *Great Rest* stress that the drug should be specifically used as a sleep aid for the sick, we surveyed known compounds which may have sedative properties or contribute to sedation. As such, we focused on the central nervous system (CNS) accessing drugs with mechanisms known to modulate alertness and wakefulness. The known percent compositions of the plants were assessed and the compounds that were observed to be sub-therapeutic at this stage were excluded from subsequent calculations. The drugs found at sufficient levels were hyoscyamine, scopolamine, morphine and codeine (morphine pro-drug).

To calculate the total possible absorption of each drug, we used modern plant composition values and calculated the total amount of drug possible based on the measurements given for 93.0 g of *Great Rest*. Afterwards, we used the percentage of bioavailability of each drug and the volumes of distribution cited in PubMed and other medical search engines to infer plasma concentrations (Appendix I). All plasma concentrations were calculated for a 70 kg person who is average and healthy.

The *Antidotarium Nicholai* recommends that the doses of *Great Rest* should be administered in chestnut sized balls. While the exact math cannot be determined, it is measured that a common chestnut radius, though highly variable, reaches a maximum of 2 cm (see Table 2). Its density could also range depending on the packing of plant mass, but for the purpose of our calculations, the conservative estimate for density of 1 g/mL is used. We were then able to use a varying dose range of chestnut radii (maximum of 2 cm) along with the conservative density estimate to describe the possible dose intended by the *Antidotarium Nicholai*. This allowed us to analyze the dosing rationale described in the text compared to the known therapeutic and lethal concentrations of each alkaloid found in the *Great Rest*. We also considered the time course of these drugs in terms of their onset of action and their half-lives found through PubMed to discuss the dosing regimen intended.

3.1. Therapeutic plasma concentrations relevant to the Great Rest

Opium (*Papaver somniferum*) ingestion can lead to analgesia, sedation, decreased gastrointestinal (GI) motility, euphoria and respiratory depression (at high doses) due to the morphine and codeine content (Fillingim et al., 2005). While morphine is known for its sedative effects, its analgesic effects may be more beneficial in the context of the *Great Rest*. Analgesia could occur without sedation and it is analgesia, not sedation, which reduces the intensity of pain felt in most illnesses leading to more 'rest' (Paqueron et al., 2002). The dose to reach analgesia of 20–40 ng/mL (0.08–0.16 mg morphine/kg per oral) of plasma was chosen to be the therapeutically relevant concentration as it is observed that sedation, which does not always occur, usually occurs prior to analgesia (Paqueron et al., 2002; Clarke and Wright, 1984; Hesselink et al., 2003).

Though hyoscyamine (from mandrake (*Mandragora officinarum* L.) and henbane (*Hyoscyamus niger* L.) help induce sedation and analgesia concomitantly with morphine, this is hard to quantify as few clinical studies have been conducted to record the combined effect of hyoscyamine, scopolamine and morphine (Kentala et al., 1998). It is also possible that hyoscyamine is used here not to cause the main sedative and analgesic effects of the *Great Rest*, but to mainly cause a disorientating effect prior to the rest-inducing analgesic effects. The ED_{50} value of 42.5 ng/mL (0.0429 mg/kg per oral) is accepted as the dose which causes the altered behavioral response leading to an inhibited thought process (Higgins et al., 1989). Hyoscyamine can also cause hallucinations, delirium, amnestic effects, disorientation, restlessness, nausea suppression and respiratory depression (Corallo et al., 2009; Ellinwood et al., 1990; Higgins et al., 1989). Peripherally, it causes tachycardia, decreased salivation, dilated pupils, suppressed tonic motility of the intestines and reduced closure of the lower esophageal sphincter (Moeller et al., 1992).

Scopolamine (from henbane (*Hyoscyamus niger* L.), the hyoscyamine derivative, is most famously known for its anti-emetic effect (Corallo et al., 2009). The ED50 to produce this effect is 6.12 ng/mL (0.00857 mg/kg per oral) (Nachum et al. 2001, 2006). It can also modulate episodic memory recall (Mintzer et al., 2010). Larger doses to produce hallucinations (0.017 mg/kg per oral or 12 ng/mL) are considered to be toxic by modern standards, but may not be considered dangerous in the context of the *Great Rest* as the dissociative effects to prevent mental processing of the disease state may also be beneficial (Corallo et al., 2009). Scopolamine is a derivative of hyoscyamine and so it behaves much like hyoscyamine (Corallo et al., 2009; Wang et al., 2011). Unlike hyoscyamine, however, scopolamine is more likely to cause amnesia, sedation and euphoria (Corallo et al. 2009). When used concomitantly with morphine, it most likely exacerbates the sedative effects of morphine and diminishes addiction to morphine (Kentala et al., 1998). Peripherally, it is less likely to lead to effects such as the reduced intestinal motility, decreased closure of the lower esophageal sphincter and tachycardia (Kentala et al., 1998). The symptoms more likely to appear are due to its more potent antisialagogue properties (dry mouth and inability to swallow well) (Kentala et al., 1998).

3.2. Lethal plasma concentrations relevant to the Great Rest

Aside from the unforeseeable dangers of hypersensitivity and allergic reactions to these drugs, the most likely lethal reaction would be due to respiratory depression (Corallo et al., 2009; Meissner et al., 2002). Respiratory depression can occur from morphine and the tropane alkaloids. An excessively high dose of morphine leads to extensive respiratory depression which could lead to death, but due to genetic variability, this response differs from person to person (Gallagher, 2010; Poulsen et al., 1996). This response occurs at an average morphine plasma concentration exceeding 200 ng/mL (0.8 mg/kg per oral), but the accepted LD_{50} in forensics is at a slightly higher dose of 240 ng/mL (0.96 mg/kg per oral) (Meissner et al., 2002).

L-hyoscyamine has not been found to be safe by the FDA and so the body of evidence for its toxicity and lethality is not as vast as that established for atropine. Atropine has been reported to be fatal near doses of 50 mg/70 kg, but there have also been accounts of survivability at 100 mg/70 kg (Corallo et al., 2009). The stringent value of 50 mg/70 kg was accepted as the LD_{50} value of atropine and since the L-hyoscyamine is the active stereoisomer, the LD_{50} value of 25 mg/70 kg (0.35 mg/kg per oral or 350 ng/mL) is used (Corallo et al., 2009; Renner et al., 2005).

Scopolamine's oral lethality is unsubstantiated in literature, but it is suggested from animal studies that the lethal dose would be larger than the lethal dose of atropine. For the purpose of this assay, the value where scopolamine causes dissociative effects will be considered as the lower threshold of toxicity; TD_{50} is 2 mg/70 kg (0.017 mg/kg per oral 12 ng/mL) (Corallo et al., 2009). Like hyoscyamine, use of scopolamine can lead to respiratory depression, but the dose for this to occur is unknown and how this drug

would quantitatively affect respiration given the other drugs simultaneously in the system is unknown as well.

4. Results

Assuming that the great rest is very well-mixed during production, morphine should begin to demonstrate an analgesic effect near 0.53 ± 0.076–1.1 ± 0.15 g of *Great Rest* ingested which corresponds to ED_{50} plasma concentration of 20–40 ng/mL or 65.9 ± 9.44–132 ± 18.9 mg of opium (Fig. 2). If there are no drug interactions, morphine becomes lethal near 5.3 ± 0.76–6.3 ± 0.91 g of *Great Rest* ingested which corresponds to 200–240 ng/mL plasma concentrations or 658.8 ± 94.4–790.6 ± 113.3 mg of opium.

Fig. 3 demonstrates that hyoscyamine's beneficial response arises after the ingestion of 1.4 ± 0.32 g of *Great Rest* which corresponds to 42.5 ng/mL or 74.9 ± 16.3 mg of henbane and 74.9 mg of mandrake. Furthermore, it suggests that the lethal response arises from ingesting 12.1 ± 2.5 g of *Great Rest* as it corresponds to 350 ng/mL L-hyoscyamine plasma concentrations or 615.1 ± 135 mg of henbane and 615.1 mg of mandrake.

The anti-emetic response due to scopolamine, on average, arises from 3.1 ± 0.1 g of ingested *Great Rest* (Fig. 4). This dose corresponds to the plasma levels of 6.12 ng/mL and 166 ± 5.56 mg of henbane. The toxic dose, that is, the dose at which hallucinations and other dissociative effects are likely to occur is at 6.1 ± 0.2 g of ingested *Great Rest* which corresponds to 12 ng/mL or 326 ± 11 mg of henbane.

As mentioned previously, the *Antidotarium Nicolai* advocates a dose the size of a chestnut. As Table 2 demonstrates, the variability of the radius of the chestnut coupled with the variability of the packing density yields a wide range of masses. It is observed that the smallest packing size of 0.5 cm radius at a density of 1 g/mL reaches the therapeutic level of all three alkaloids, but doubling the size of the radius reaches the lethal level of morphine.

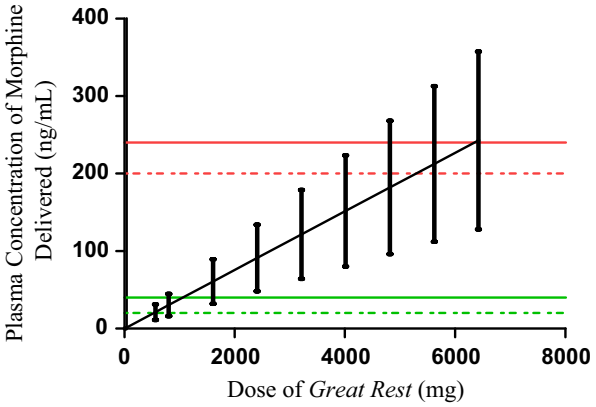

Fig. 2. Plasma concentrations of morphine from opium after the ingestion of the *Great Rest*.

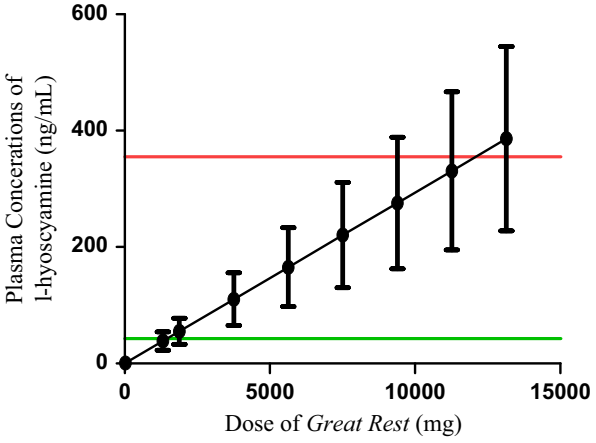

Fig. 3. Plasma concentrations of L-hyoscyamine from henbane and mandrake after the ingestion of the Great Rest.

Table 2
Plasma concentrations delivered with different masses of the *Great Rest*.

	All of the *Great Rest*	Smallest likely chestnut size	Medium chestnut size	Large chestnut size	Largest chestnut size	ED_{50} (ng/mL)	LD_{50} (ng/mL) or TD_{50} (ng/mL)
Radius of chestnut	4	0.5	1	1.5	2	-	-
Mass of "chestnut" (g)	93	3.4	7.5	15.5	46.5	-	-
Divisions of Batch	1	27	12	6	2	-	-
Total	3517.7	128.6	293.1	586.0	1748.6	**20 to 40**	**200 to 240**
Morphine delivered (ng/mL)							
Scopolamine delivered (ng/mL)	182.2	6.7	15.2	30.4	91.1	**6.12**	**12**[1]
Hyoscyamine content (ng/mL)	2663.4	98.6	222.0	443.9	1331.7	**42.5**	**350**

1. **This value is the toxic dose value, not the lethal dose value.**
Green=Therapeutic and Safe **Orange= Toxic, but not lethal**
Red=Potentially Lethal **Grey= Reference value**

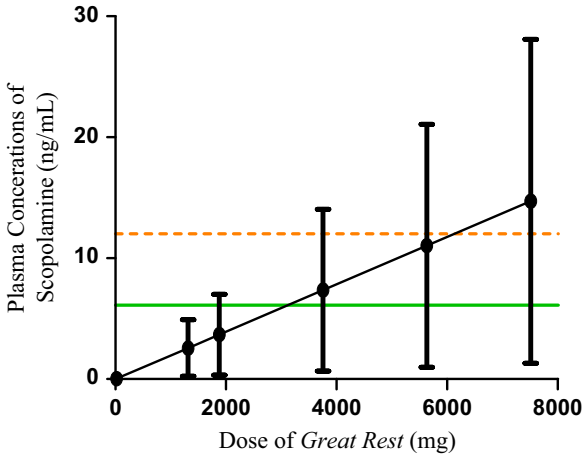

Fig. 4. Plasma concentrations of scopolamine from henbane after the ingestion of the *Great Rest*.

5. Discussion

5.1. Efficacious doses

It is suggested that the minimum dose of the *Great Rest* required to cause an analgesic effect is 0.53 ± 0.076 g for a standard 70 kg person (Fig. 2, Table 3). This is the lowest possible dose of *Great Rest* required to cause a physiologically recognized CNS-mediated effect. This response is largely due to the codeine and morphine from the 65.9 ± 9.44 mg of opium. (Table 3).

The responses which would arise due to the tropanes include the anti-emetic effect of scopolamine which requires 3.1 ± 0.1 g of *Great Rest* (166 ± 5.56 mg of henbane) and the disorienting effects of L-hyoscyamine which requires 1.4 ± 0.32 g of *Great Rest* (74.9 ± 16.3 mg of henbane and 74.9 mg of mandrake) (Figs. 3 and 4, Table 3) (Higgins et al., 1989). At doses below 1.4 ± 0.32 g, there should be no effect due to the tropanes as they would both be at sub-therapeutic levels however; morphine would still elicit an effect. At doses between 1.4 ± 0.32 g and 3.1 ± 0.1 g, morphine will demonstrate a response and there may be the anti-emetic effect from scopolamine, but there should be no effect due to L-hyoscyamine. While both of the tropanes reach therapeutic concentrations at doses of 3.1 ± 0.1 g to 5.3 ± 0.76 g of ingested *Great Rest*, all three compounds elicit an effect in *Great Rest*. Although the plasma concentration of morphine is not lethal, it is very substantial.

5.2. Toxic and lethal doses

Morphine starts to become lethal when 5.3 ± 0.76–6.3 ± 0.91 g of *Great Rest* is ingested which corresponds to 658.8 ± 94.4–790.6 ± 113.3 mg of opium (Fig. 2; Table 4; Meissner et al., 2002). At 6.1 ± 0.2 g of *Great Rest* or 326 ± 11 mg of henbane, hallucinogenic effects of scopolamine become pronounced, but it is not lethal at this dose; it is lethal at a dose exceeding hyoscyamine's lethal dose (Fig. 3; Table 4). Hyoscyamine is suggested to be lethal after the ingestion of 615.1 ± 135 mg of henbane and 615.1 mg of mandrake or 12.1 ± 2.5 g of *Great Rest* (Fig. 4; Table 4) which indicates that it is not as lethal as morphine. Scopolamine is thought to be lethal at a dose greater than hyoscyamine's dose and so it is probable that scopolamine is not the limiting drug.

While lethality due to the *Great Rest* cannot be fully described as the drug interactions are not extensively recorded and many compounds were not assayed, our data suggests that the limiting compound is morphine. It is observed that morphine is lethal at a dose of 5.3 ± 0.76–6.3 ± 0.91 g of *Great Rest*, which is roughly double of 3.1 ± 0.1 g, the dose where all three compounds are efficacious.

Chronic morphine use can lead to morphine tolerance and it is possible that the lethal dose would be larger for certain people, but it is also possible that as tolerance developed, the unbearable effects of scopolamine became more pronounced, deterring the patient from consuming more *Great Rest*. Additionally, in a conditioned placed preference experiment conducted on mice, scopolamine diminished morphine-seeking behavior. This indicates that scopolamine may decrease chronic morphine consumption (Kentala et al., 1998).

5.3. Temporal kinetics of the alkaloids in the Great Rest

Due to the nature of unsupervised administration and unregulated dosing, it is possible that a patient would self-administrate multiple doses of the *Great Rest* to achieve the desired effects of opium. Morphine is administered for its sedative and analgesic

Table 5
Time course of drugs in blood.

Drug	Onset (h)	Peak plasma (h)	$t_{1/2}$ life (h)
Hyoscyamine	0.3–0.5	0.5–1	3.5–4.2
Scopolamine	~0.5	0.5	4.5
Morphine	1–2	1–2	2–3

Table 3
Summary table of the *Great Rest* doses required to elicit therapeutic levels of the alkaloids.

Compounds	ED_{50} (ng/mL)	Mass of *Great Rest* to achieve ED_{50} (g)	Plant mass required to achieve ED_{50} (mg)
Morphine	20–40	0.53 ± 0.076 to 1.1 ± 0.15	65.9 ± 9.44 to 132 ± 18.9 of opium
Scopolamine	6.12	3.1 ± 0.1	166 ± 5.56 of henbane
L-hyoscyamine	42.5	1.4 ± 0.32	74.9 ± 16.3 of henbane and 74.9 of mandrake

Table 4
Summary table of the *Great Rest* doses required to elicit toxic or lethal levels of the alkaloids.

Compounds	LD_{50} (ng/mL) or TD_{50} (ng/mL)	Mass of *Great Rest* to achieve LD_{50} or TD_{50} (g)	Plant mass required to achieve LD_{50} or TD_{50} (mg)
Morphine	200–240	5.3 ± 0.76 to 6.3 ± 0.91	658.8 ± 94.4 to 790.6 ± 113.3
Scopolamine	12	6.1 ± 0.2	326 ± 11 of henbane
L-hyoscyamine	350	12.1 ± 2.5	615.1 ± 135 of henbane and 615.1 of mandrake

effects, but it only begins to take effect one to two hours post-ingestion (Table 5; Collins et al., 1998). Hyoscyamine and scopolamine, on the other hand, can begin to take effect as quickly as 20 min post-administration (Higgins et al., 1989). We propose that henbane and mandrake are administered for their predominant dissociative effects which would deter the self-administering patient from taking a second dose of the *Great Rest* before the onset of morphine thereby reducing the possibility of overdosing on morphine. Aside from the disorienting effects of the tropanes, the anti-nausea effects of scopolamine would also have been quite beneficial during a fever and would have likely alleviated the nausea sensation associated with some fevers.

Following first order kinetics, morphine would last 10–15 h in the system, while hyoscyamine and scopolamine would last 17.5–21 and 22.5 h respectively (Berkowitz et al., 1976; Kamimori et al., 1990;, Putcha et al., 1989). The onset of action and peak plasma levels may be modulated by other compounds and food. Nicholas appears to have been aware of this effect when he comments that when the *Great Rest* is administered "to men who are almost healthy, they really must eat or dine in a regular manner". Drug administration with food changes the onset of action and peak plasma levels as the gastric emptying rate along with the bulk of the food may reduce the rate of absorption of these drugs (Welling, 1996).

6. Conclusion

Given the limitations of this analysis, there are multiple variables which may affect our conclusion. The plants' compositions were assessed using modern values which may not reflect the plant variants described in this recipe. Furthermore, the maintenance of these plants as well as the percent composition of each drug not analyzed is unknown which may lead to false conclusions. The genetic background of the population intended for treatment was not examined and for most of the calculations, the standard weight of a 70 kg person was used (Poulsen et al., 1996). Also, the intended population is ill and it is known that enzymes fluctuate during illnesses such as fevers which modifies plasma concentrations of the drugs. This may lead to discrepancies and misrepresentations of the true doses of these drugs in the intended population. Finally, all calculations conducted in this analysis assumed complete equal distribution of the compound in the production phase, complete absorption of the compounds from the gastrointestinal tract and enzyme levels of healthy populations.

Our review of modern pharmacological studies of morphine, hyoscyamine and scopolamine demonstrates that tropane use with morphine may be beneficial as it increases sedative effects, deters the user from self-administering multiple doses in a short period of time, and diminishes opiate addiction (Kentala et al., 1998). In addition, this analysis suggests that the dosing of the *Great Rest* and the directions of the *Antidotarium Nicolai* follow the known physiological effects of the alkaloid compounds. We demonstrate that the optimal dose of the *Great Rest* of 3.1 ± 0.1 g would have proved beneficial for the majority of patients. The lethal dose from 5.3 ± 0.76 g to 6.3 ± 0.91 g of *Great Rest* is double the efficacious dose and this indicates that lethality may have been avoidable. The chestnut size is likely to be 3.1 g which would yield 27 chestnuts of *Great Rest* and that the dosing and instructions discussed by Nicholas seem to reflect empirical logic.

Our analysis demonstrates that medieval compound drugs can be analyzed with recourse to modern pharmacological studies, a type of inquiry we might term "historical pharmacology". It is likely that other drugs popular for centuries, such as those found in the *Antidotarium Nicolai* or in other sources considered to be authoritative, reflect experimental knowledge and pharmacological insight well worth viewing through the lens of modern pharmacology.

Appendix

Bioavailability calculations

Morphine

Morphine and codeine are found in opium at concentrations of $14 \pm 5\%$ w/w and $5.9 \pm 1.9\%$ w/w respectively (Remberg et al. 2008). Due to morphine's biovailability of $23 \pm 8\%$ and codeine's biotransformation to morphine of 90%, post-metabolism, $3.2 \pm 1.5\%$ w/w morphine is absorbed from opium and $5.3 \pm 1.7\%$ w/w of morphine from codeine reaches the system (Stuart-Harris et al. 2000; Laneury et al. 1998; Poulsen et al. 1996). Altogether, $8.5 \pm 2.3\%$ w/w morphine gets into the system from ingesting opium and its high volume of distribution indicates it distributes fully (4.0 ± 2.3 L kg^{-1}) (Hoskin et al. 1989).

Hyoscyamine

The bioavailability of hyoscyamine is accepted as being equivalent to atropine; it is 50% bioavailable (Ali-Melkkilä et al. 1993). However, it is suggested that its metabolizing enzymes prefer the levo-enantiomer which may indicate a discrepancy in the accepted bioavailability of hyoscyamine (Van Der Meer et al. 1986). Its high volume of distribution of 1.01 L kg^{-1} suggests that it distributes fully in the system and that it crosses the blood brain barrier (Kanto et al. 1981).

Mandrake (*Mandragora officinarum* L.) has 0.2% w/w tropane content, but the exact composition is not known (Peduto 2001). Due to lethality being more likely for hyoscyamine than scopolamine in animal studies, we consider the content to be exclusively hyoscyamine to make conservative estimates (Janowsky et al. 1985; Wang et al. 2011). On average, modern henbane contains $7.6 \pm 3.2\%$ w/w of hyoscyamine (Bahmanzadegan et al. 2009). After hyoscyamine's absorption from both plants, $3.9 \pm 1.6\%$ w/w gets into the system.

Scopolamine

The oral absorption of scopolamine is, on average, only 2.6% and it distributes fully as indicated by its high volume of distribution of 1.4 ± 0.3 L kg^{-1} (Renner et al. 2005; Putcha et al. 1989). Modern henbane variants contain $9.9 \pm 9.0\%$ w/w of hyoscyamine (Bahmanzadegan et al. 2009). After the metabolism of L-hyoscyamine, $0.26 \pm 0.23\%$ w/w gets into the system from henbane.

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