

# The mystery of Juliet's death after Romeo's kiss. Romeo had drunk a powerful venom

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Sir,

Before to begin this dissertation it is better to explain three important physiological and chemical behaviours, that could embody finally the simplest explication of this strange pharmacological demeanour.

- a) The benzodiazepines nitrazepam and clonazepam were found to be unstable in saliva at room temperature and nitrazepam was converted into 7-aminonitrazepam. The conversion rate of nitrazepam was strongly dependent on the composition of the subject's saliva, and for this reason both nitrazepam and clonazepam did not induce a real drowsiness in the woman who underwent the cunnilictus [1].
- b) There exist a racial difference: some A.A. referred that individual differences exist between patients, and, for topical therapy, differences in skin due to race had be taken in consideration. Pharmacological response depends upon the percutaneous absorption and the inherent activity of the chemical once absorbed into the biological system. Our objective was to determine the in vivo percutaneous absorption of three test chemicals in human subjects with Asian (A), black (B) and Caucasian (C) ethnic skin. Following a 30 min topical application on the upper outer arm of 1 Mmol/cm <sup>214</sup>C-labeled chemical, percutaneous absorption was determined by both urinary excretion and the stripping technique. Amounts absorbed were: for benzoic acid 1.43 ± 0.27% (SD) (A), 1.07 ± 0.18% (B), 1.2 ± 0.19% (C); for caffeine 1.06 ± 0.17% (A), 1.01 ± 0.19% (B) and 0.96 ± 0.12% (C); for acetylsalicylic acid 1.8 ± 0.31% (A), 1.59 ± 0.31% (B) and 2.12 ± 0.36% (C). No statistical difference ( $P > 0.05$ ) was found in percutaneous absorption of benzoic acid, caffeine

or acetylsalicylic acid between Asian, black and Caucasian subjects [2-7].

- c) There are physiological and physipathological factors to be observed before experimentations. Factors related to the vaginal physiology include pH of vagina (3.5 to 4.9), effect of the estrus cycle on the permeability of the vaginal mucosa, thickness of vaginal epithelium, vaginal fluid volume, chemical composition of fluid, pH, viscosity and surface tension and the pressure exerted on the dosage form by the rectal wall, play a vital role in vaginal drug absorption and sexual arousal, mucociliary clearance (MCC), vaginal obstruction, etc. which affect either the mucus or ciliary heating and vaginal blood flow. 2) Physicochemical Factors: Factors related to the dosage forms are physicochemical characteristics of the active ingredients; pH and mucosal irritancy; osmolarity; viscosity (solution, gels) and density (powder, tablet) to the formulation; concentration and volume administration; and type of dosage forms; particle size of the molecule of drug, hydrophilicity or lipophilicity of drug molecule, molecular weight of drug molecule, chemical nature, ionization surface charge, etc.

In tables was presented the list of the benzodiazepines and their relative half lives the A.A (Table 1) and the hours of drowsiness induced in the women after having undergone the cunnilictus (Table 2).

It is very odd the phenomenon that the longer is the half life of the benzodiazepines, the shorter is the induced drowsiness in the woman.

Exhaustive efforts have been made toward the administration of drugs, via alternative routes, that

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**Table 1:** All the kinds of hypnotics the AA assumed to make their proofs

Type of benzodiazepines	Half life (h) of the benzodiazepines
Bromazepam	20-40
Cinazepam	4-5
Cinolazepam	60
Clonazepam	9
Diclazepam	10-18
Estazolam	42
Etizolam	10-31
Flubromazepam	6
Flunitrazepam	100-220
Lorazepam	9.5-20
Metizolam	12
Nimetazepam	14-30
Nitrazepam	17-48
Quazepam	120
Temazepam	10
Triazolam	2

**Table 2:** The hours of drowsiness induced in the women after having undergone the cunnilictus

Case	Hours of induced drowsiness in woman
I	3
II	4
III	8
IV	0.30
V	2
VI	3
VII	5
VIII	1
IX	3
X	4
XI	2
XII	3
XII	0
XIV	1
XV	6
XVI	2

are poorly absorbed after the oral administration. The vagina as a route of drug delivery has been known since ancient times. In recent years, the vaginal route could be rediscovered as a potential route for systemic delivery of benzodiazepines and other therapeutically

important macromolecules. However, successful delivery of drugs through the vagina remains a challenge, primarily due to the poor absorption across the vaginal epithelium [7].

It is quite interesting to notice that Case IV (Clonazepam) that has been destroyed by saliva is not able to induce drowsiness in the woman. Nitrazepam too is inactive at all.

## Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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