Physiologically-based pharmacokinetic modeling of amantadine and acetylamantadine metabolites for potential applications as cancer biomarker

Eman Alraddadi and Donald Miller

Department of Pharmacology and Therapeutics, The Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada

Background

Cancer is the second leading cause of death globally. Despite advances in treatment, there is a need for faster and economical screening tests for early diagnosis of cancer. Spermidine/spermine N^1-acetyltransferase (SSAT-1), an enzyme involved in the homeostasis of the polycationic aliphatic amines, spermine and spermidine, is overexpressed in many types of cancer cells. Amantadine is an FDA and Health Canada approved drug that is acetylated by SSAT-1 producing acetylamantadine, a terminal and stable end product excreted in urine (Figure 1). Recent studies suggest that that SSAT-1 based acetylation of amantadine could serve as a biomarker for lung cancer. However the SSAT-1 expression and activity within tumor compartments required to produce the reported levels of acetylamantadine as well as the potential use of amantadine for detection of tumor in other tissues is unclear.

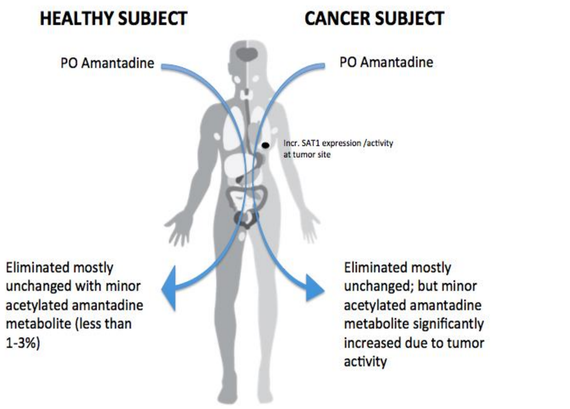


Figure 1. Acetylamantadine elimination in healthy vs. cancer subjects.

Objective

Use physiologically-based pharmacokinetic modeling to determine plasma profile and tissue distribution of amantadine and identify conditions required for achieving acetyl amantadine levels in patients with tumor.

Methods

Physiologically-based pharmacokinetic modeling was performed using Gastroplus™. This module simulates and predicts pharmacokinetic (PK) profiles of compounds using input parameters based on the physicochemical properties (e.g., solubility, LogP, pKa) of the compound and species-specific physiological disposition properties (e.g., Vd , blood flow and renal and metabolic clearance rates). The modeling program consisted of various tissue compartments, including the heart, lung, liver, spleen, gastrointestinal tract, adipose tissue, skeletal muscle, brain, kidney, skin, reproductive organs linked together by venous and arterial blood circulation. Plasma and tissue compartment kinetics for amantadine (200 mg PO) was simulated in humans and compared to previous observed values. Once the initial PK parameters for amantadine were established, a 5 ml tumor compartment was introduced to the model and simulations were performed to predict acetyl amantadine levels using SSAT-1 enzyme expression in normal tissues and various cancers (Figures 2 and 3).

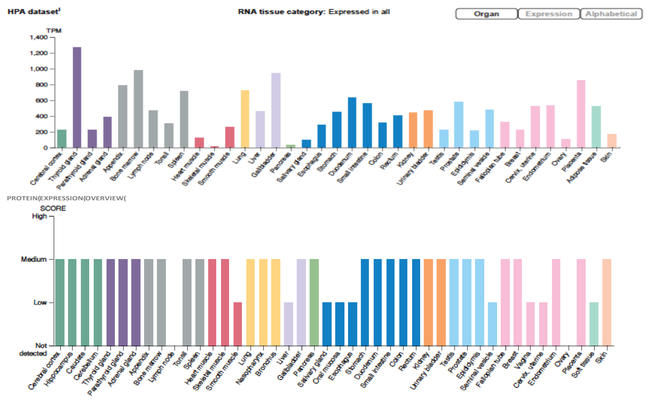


Figure 2. SSAT-1 tissue RNA and protein expression under normal conditions. Data obtained from the human protein atlas public database, www.proteinatlas.org

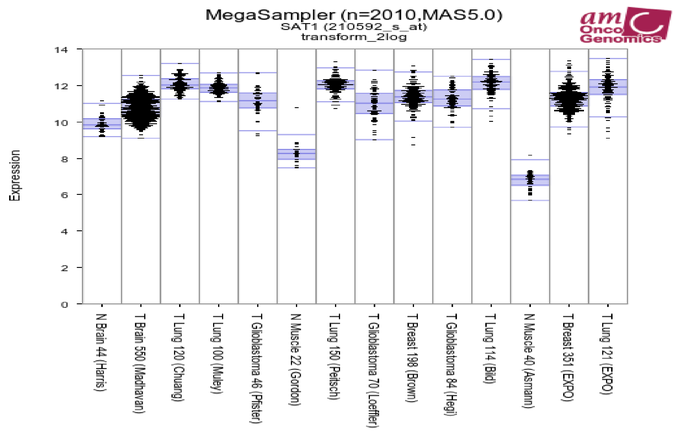


Figure 3. SSAT-1 gene expression in various cancers. Values were obtained from R2: Genomics Analysis and Visualization Platform. http://r2.amc.nl

Results

- Plasma and tissue compartment PK for amantadine (200 mg po) was modeled in humans using a perfusion limited distribution model (Figure 4). Comparison of plasma PK parameters to previous studies are shown in Table 1.

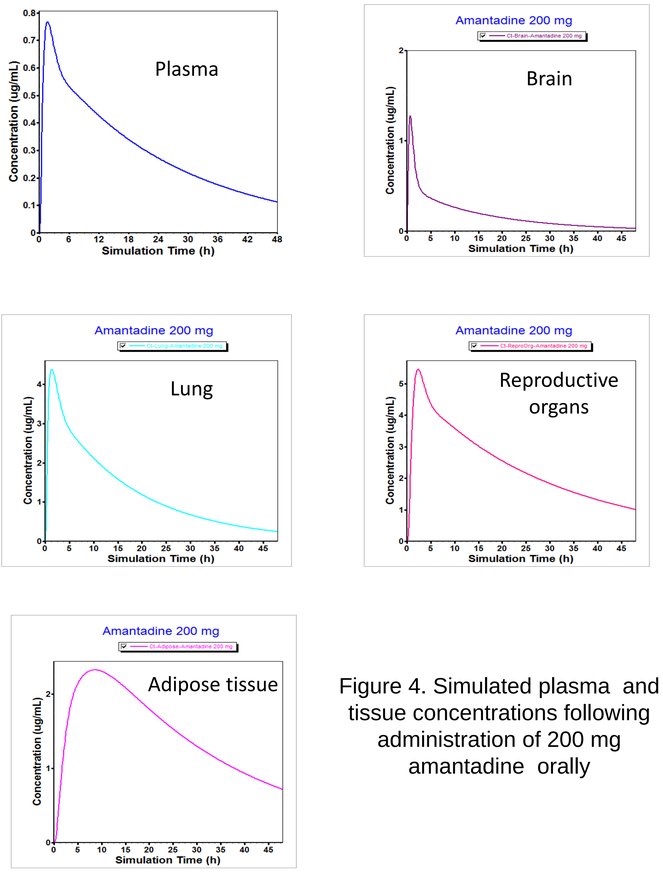
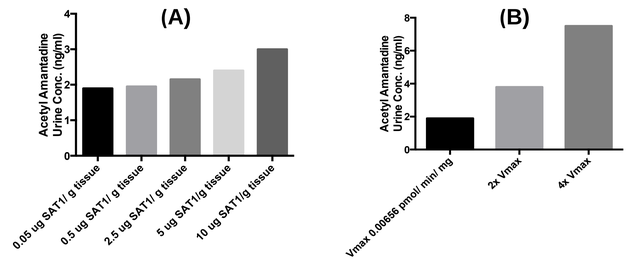


Figure 4. Simulated plasma and tissue concentrations following administration of 200 mg amantadine orally

	C_{max} (µg/ml)	T_{max} (hours)	Half-life (hours)	Clearance (L/hr)
Simulated values	0.78	1.4	12.3	7.3
Observed Values	0.718 ± 0.098	2	11.5 ± 1.8	6.6 ± 1.2

Table 1.Simulated vs observed amantadine PK parameters.

- Based on low to moderate SSAT1 expression in normal tissue, urine and plasma concentrations of acetylamantadine at 2 hours was 1.9 and 0.08 ng/ml, respectively (Figure 5 and Figure 6).
- Increasing SSAT-1 expression within the tumor compartment had minimal impact on acetylamantadine levels in the urine and plasma (Figures 5A and 6A). On the other hand, changing the activity of the enzyme by increasing Vmax by 2 fold and 4 fold in the tumor compartment, urine and plasma levels of acetylamantadine increase up to 8 and 0.35 ng/ml, respectively (Figures 5B and 6B).



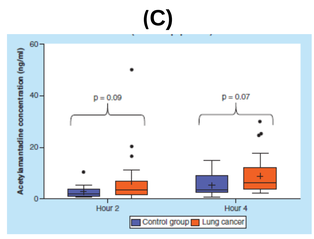


Figure 5. 2-Hr simulated urine concentrations of acetylamantadine following (A) increasing SSAT-1 expression or (B) increasing Vmax. (C) Observed acetylamantadine urine concentrations at 2 and 4 hours in normal vs lung cancer subjects (taken from Future Sci OA (vol 5(2), 2018)

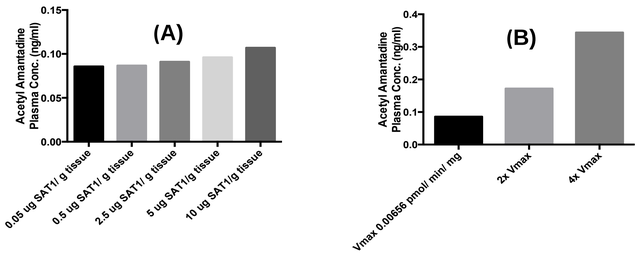


Figure 6. Simulated plasma concentrations of acetylamantadine following (A) increasing SSAT-1 expression or (B) increasing Vmax

Conclusion

- Current modeling parameters provided comparable PK parameters to observed values for amantadine.
- Extensive distribution of amantadine was observed in all tissues modeled, suggesting potential applications for tumor detection in multiple tissues.
- The levels of acetylamantadine observed in lung tumor patients most likely reflect changes in SSAT1 activity within the tumor site

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