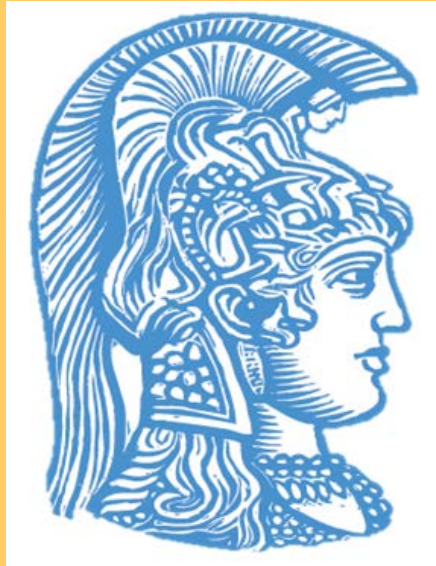


Hyperhydration may alter urine pharmacokinetic profile of drugs: A simulation study using budesonide as model drug



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Introduction

Budesonide (BDS), a non-halogenated glucocorticosteroid, is characterized by potent local anti-inflammatory activity and was initially introduced for the treatment of asthma and rhinitis. In sports, all glucocorticosteroids are prohibited in-competition by the World Anti-Doping Agency (WADA) [1] when administered by oral, intravenous, intramuscular or rectal routes. According to the statistics reported by the WADA accredited laboratories, BDS was the glucocorticosteroid with most number of adverse analytical findings in recent years, representing 43% of reported cases within this class of compounds [2].

Objectives

To study the effect of hyperhydration on the urine pharmacokinetic profile of the model drug BDS and its possible implication as a doping masking procedure used by athletes.

Methods

Population Pharmacokinetic (PK) Analysis

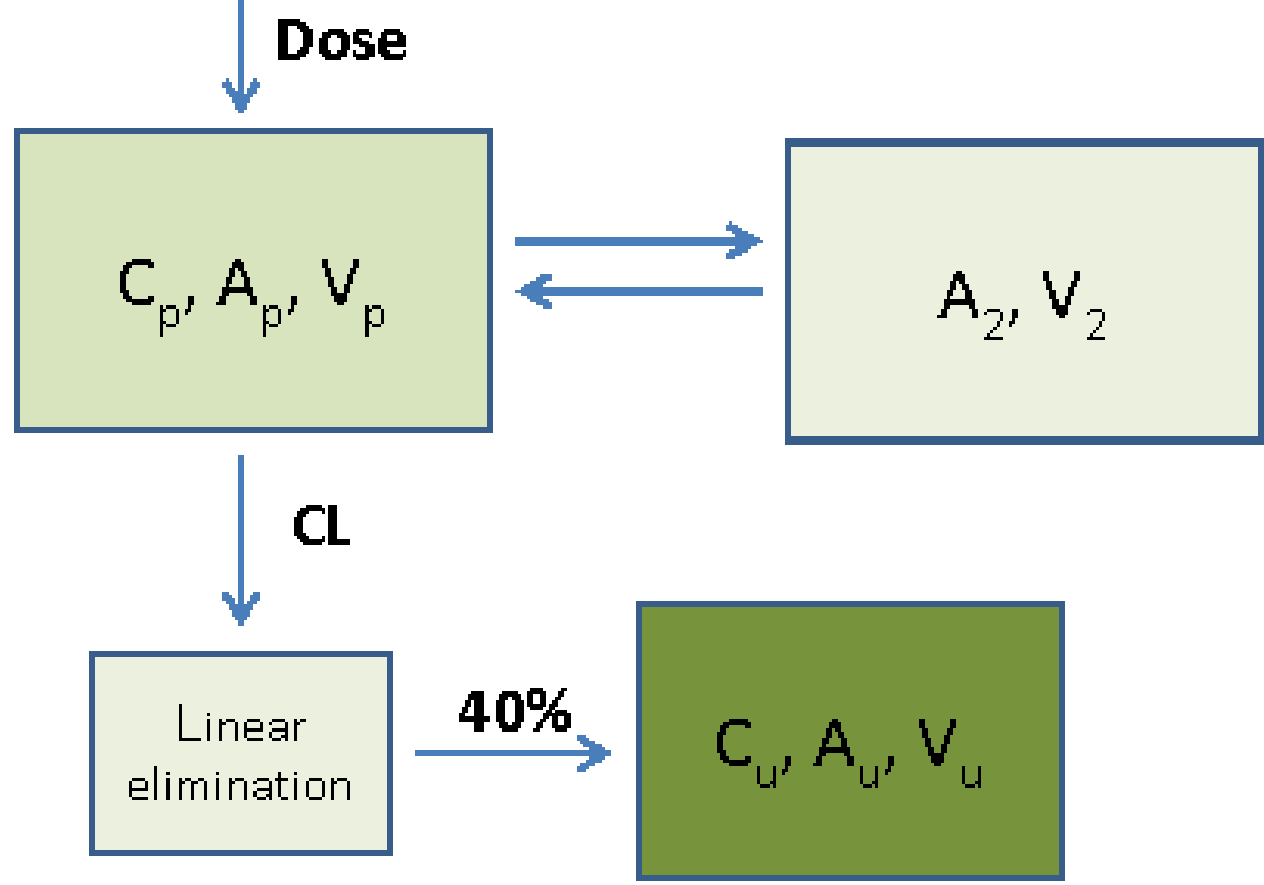
Data from a bioequivalence study of BDS, after oral administration of 3 mg to 6 healthy volunteers were analyzed. Population PK analysis was performed with FOCE method with interaction in NONMEM V7.2.0 [3]. Different structural models were considered and model selection was based on the reduction of the objective function for nested models, and goodness of fit plots.

Table 1: PK parameters estimates.

PK Parameter	Value	Variance	PK Parameter	Value	Variance
CL (litter/h)	1060	0.204	Tlag (h)	0.3	-
V (litter)	2380	0.286	Covariance CL-V	0.138	
ka (1/h)	1.69	0.378	Correlation CL-V	0.57	

Simulations

1000 subjects administered single per os dose of 9 mg BDS were simulated, using MatLab SimBiology toolbox, by a one-compartment popPK model:



Scheme 1: Schematic representation of the pharmacokinetic model (C_p , A_p , V_p) used in conjunction to the urine compartment (C_u , A_u , V_u).

BDS is excreted primarily as metabolites in the urine and feces. The resulting major metabolites of BDS are 16 α -hydroxyprednisolone and 6 β -hydroxybudesonide.

Renal elimination of unchanged BDS is low because of its extensive biotransformation in the liver.

In healthy adults, 60% of an intravenous radiolabeled BDS dose was recovered in urine in the form of the corresponding metabolites.

Urine production was modelled based on the renal regulation of urine volume [5] and the conditions of water retention [4].

According to the circadian pattern of urine production and the normal water balance, 24 h were divided in three intervals simulating a urine sampling collection schedule in order to evaluate the effect of hyperhydration (**Table 2**).

Diurnal variation on urine output and rate production was modelled using data regarding the renal response to an acute water load [4].

Table 2: Calculation of urine rate production (ml/min) and water excretion (%) during 24 h.

Variable	Time			
	07:00-15:00 (1st interval)			Total
	07:00-10:00 (180 min)	10:00-12:00 (120 min)	12:00-15:00 (180 min)	
Fluid Intake, ml	622	415	622	1659
Urine Output, ml	267	178	267	713
Urine rate, ml/min	1.49	1.49	1.49	-
%(Urine output/Fluid intake)	43%	43%	43%	-

Variable	15:00-23:00 (2nd interval)			Total
	15:00-18:00 (180 min)	18:00-20:00 (120 min)	20:00-23:00 (180 min)	
	Fluid Intake, ml	504	336	504
Urine Output, ml	425	283	425	1133
Urine rate, ml/min	2.36	2.36	2.36	-
%(Urine output/Fluid intake)	84%	84%	84%	-

Results

- ✓ BDS urine concentration follows the circadian rhythm of urine production regardless of hydration state (**Fig. 2A**).
- ✓ A significant decrease on BDS concentrations at early times after hyperhydration was observed compared to the normal profile (**Table 3, Fig. 1B-D**); the difference was more pronounced with hyperhydration administered twice daily and also as the hydration level increased (**Table 3**).
- ✓ BDS concentrations below minimum required performance limit (**MRPL, 30 ng/mL**) resulting in no reportable cases according to WADA guidelines are observed not only after hyperhydration at all hydration levels but even in the normal PK profile attributed to the circadian rhythm of urine production (**Table 4**).

Table 3: BDS concentration decrease (%) at early time points after hyperhydration at all hydration levels compared to normal urine profile.

% BDS Concentration Decrease									
Day	Hyperhydration administered once daily			Hyperhydration administered twice daily					
	10%	50%	90%	10%		50%		90%	
Low Hydration Level	--37.2	-40.1	-43.3	-36.4	-47.2	-38.6	-52.0	-43.1	-57.1
Medium Hydration Level	-69.8	-69.5	-71.9	-69.9	-74.0	-70.8	-75.8	-70.5	-77.0
High Hydration Level	-79.6	-79.6	-80.5	-78.6	-83.2	-79.6	-84.0	-80.8	-86.1

Table 4: Percentage (%) of BDS urine concentration values below the MRPL (30.0 ng/mL) according to WADA guidelines for the administered dose after single and double hyperhydration and for the normal urine C-t profile.

Hydration Level	
Normal	50.5
Low (single)	50.5
Medium (single)	50.1
High (single)	50.8
Low (double)	50.6
Medium (double)	51.4
High (double)	51.2

Figure 1: Simulated BDS plasma concentration (ng/mL)-time (h) profile.

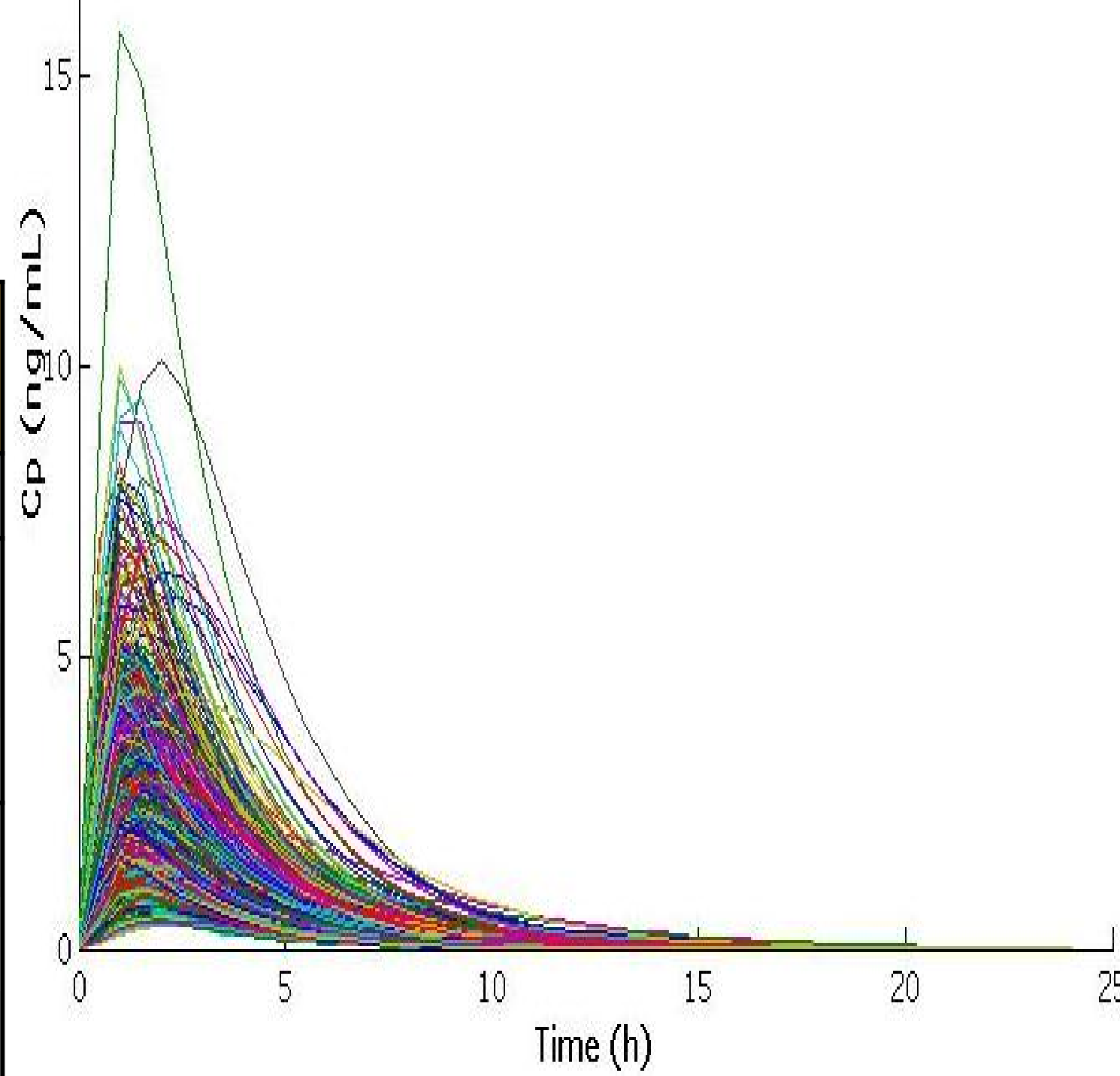
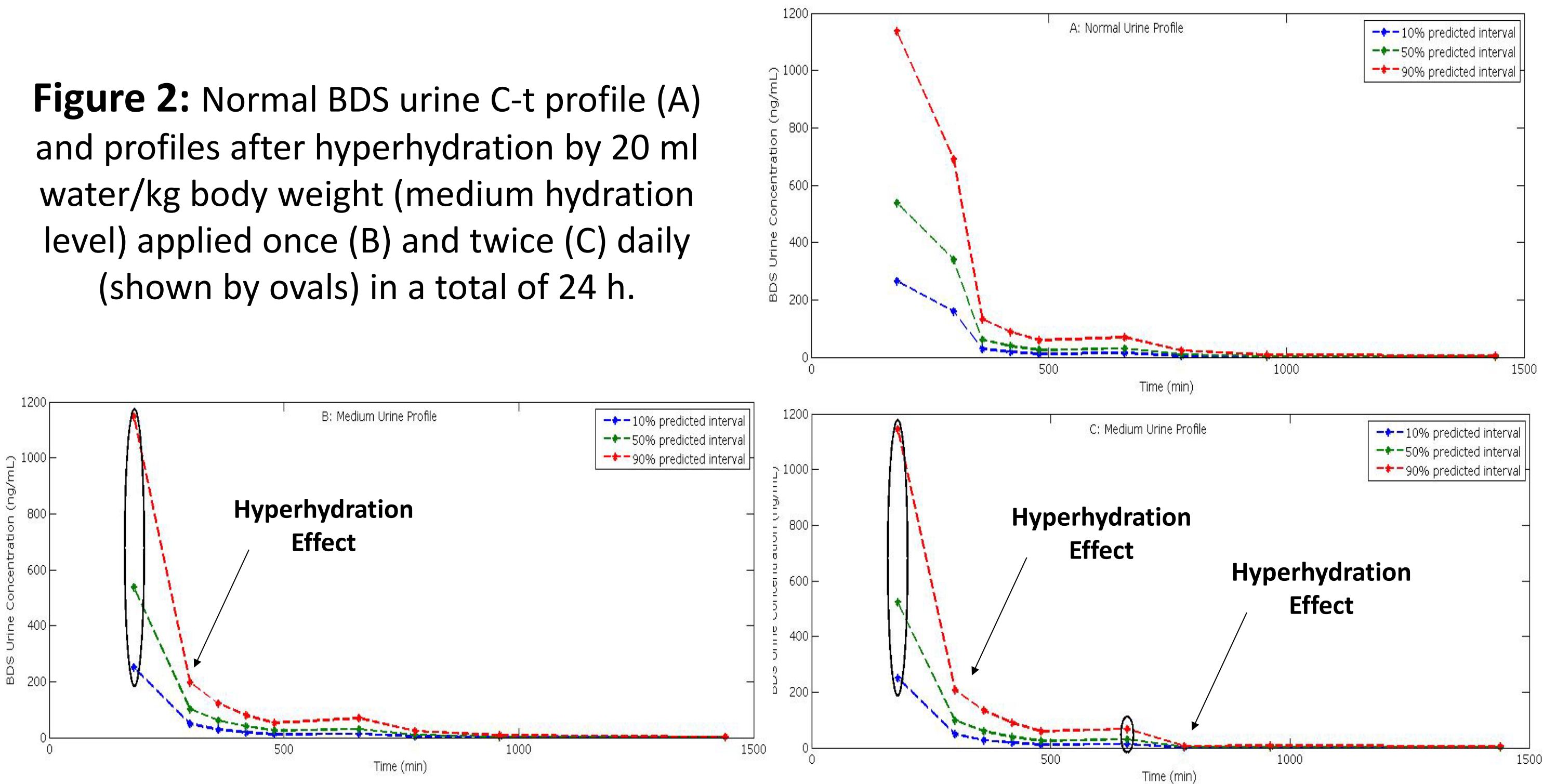


Figure 2: Normal BDS urine C-t profile (A) and profiles after hyperhydration by 20 ml water/kg body weight (medium hydration level) applied once (B) and twice (C) daily (shown by ovals) in a total of 24 h.



Conclusions

Clear effect of hyperhydration on BDS urine profile was shown, supporting the hypothesis of its possible application as a doping masking procedure by athletes. These findings may lead to optimal design of the time schedule of urine sampling during anti-doping control allowing the detection of doping agents if hyperhydration could be used by athletes as a masking procedure. To verify this hypothesis, a single dose BDS PK study in healthy male athletes with or without hyperhydration is designed, based on the present simulation analysis.

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