Pharmacometrics-based analysis of salmeterol and α-hydroxysalmeterol in plasma and urine: practical implications for doping control

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Background

- Salmeterol is a commonly used β_2-agonist included in the List of Prohibited Substances and Methods of the World Anti-Doping Agency (WADA) with a specified dosing limit of 200 µg per 24h period via inhalation administration.[1]
- A urine **minimum reporting level (MRL)** of 10 ng/mL is currently considered as suggesting misuse/doping.

Objectives

- To develop a population pharmacokinetic model describing the concentration-time profiles of salmeterol and its major metabolite α-hydroxysalmeterol in plasma and in urine.
- To evaluate the ability of the current WADA MRL-based approach to discriminate between permitted and prohibited use of salmeterol.

Methods

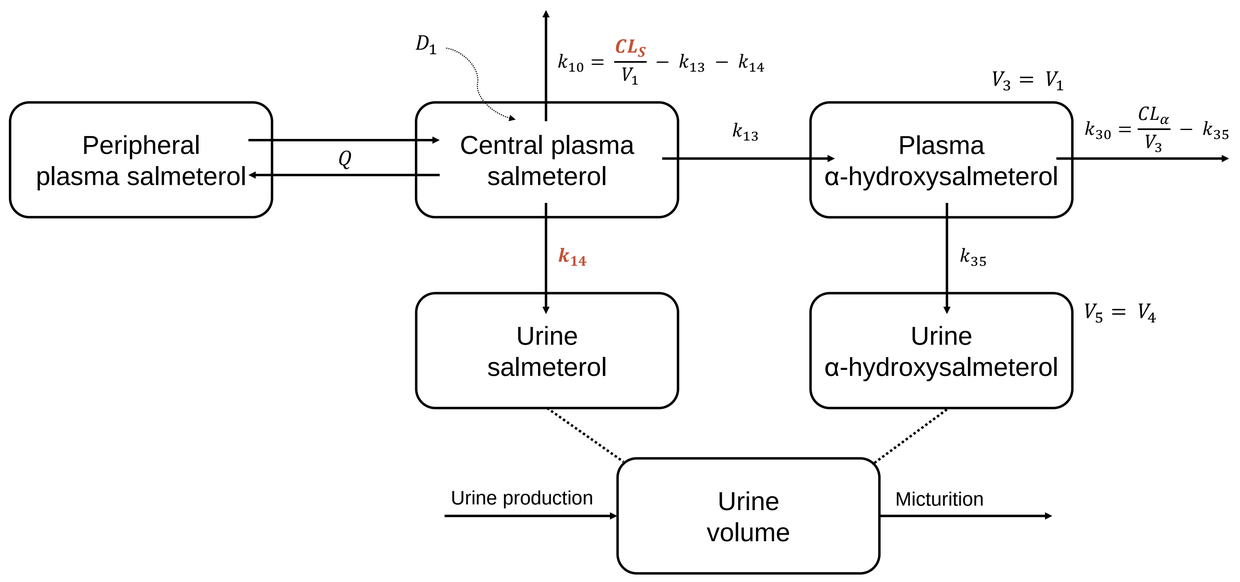
- Individual data were obtained from studies on inhaled salmeterol disposition sponsored by WADA.
- Urine concentrations were corrected using the urine specific gravity (SG) when available according to WADA guidelines.[2]
- Because urine volumes were only recorded for some subjects, a separate urine compartment was defined to approximate physiologic micturition assuming constant urine production.
- Simulations were performed to evaluate how different dosing regimens administered every 12h for one week affect salmeterol urine concentrations.

Results

A total of 1175 concentrations measured in 92 individuals were obtained from five published[3-7] and one unpublished studies:

Studies available	n	Type of individuals	Study plan	Concentrations available	Urine volume	SG
Jacobson *et al.* [3]	7	Healthy	100 µg SD	52 urine salmeterol	-	✓
	14	Athletes	200 µg SD	57 urine α-hydroxysalmeterol		
Jessen *et al.* [4]	11	Athletes	Trial 1: 400 µg single dose Trial 2: washout + 200 µg SD Trial 3: 200 µg for 7 days	179 plasma + 106 urine salmeterol 185 plasma + 106 urine α-hydroxysalmeterol	✓	✓
Jacobson *et al.* [5]	10	Healthy	50 µg SD (n=6) 200 µg SD (n=4)	39 urine salmeterol	-	-
Hostrup *et al.* [6]	10	Healthy	100 µg SD	60 plasma + 60 urine salmeterol	-	✓
	10	Asthmatics		60 urine α-hydroxysalmeterol		
Deventer *et al.* [7]	6	Healthy	100 µg SD	37 urine salmeterol	✓	-
Petrou *et al.* (unpublished)	24	Healthy	Trial 1: 100 µg SD Trial 2: washout + 100 µg SD	36 plasma + 104 urine salmeterol 94 urine α-hydroxysalmeterol	-	✓

SD: single dose

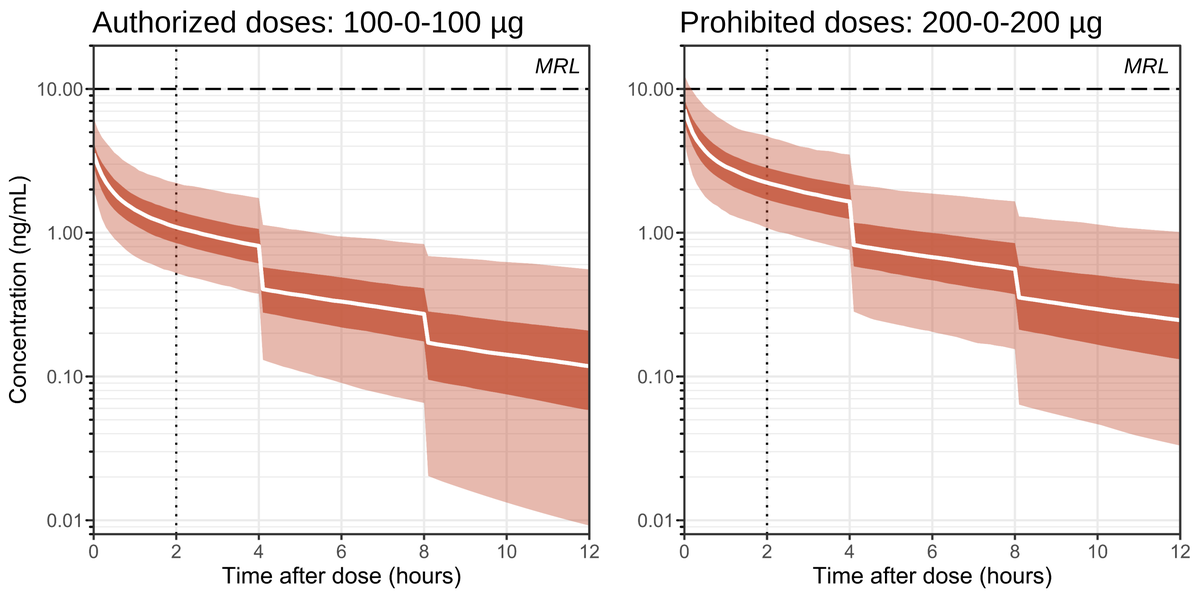


Parameters	Final model		Bootstrap (n=2000)	
	Estimate (RSE, %)		Median [$CI_{95\%}$]	
V_1 (L)	**446**	**(17)**	**446**	**[356 – 524]**
ω_{V_1} (CV%)	16.3	(54)	15.5	[4.8 – 22.2]
Q (L/h)	**1490**	**(22)**	**1443**	**[1121 – 2144]**
ω_Q (CV%)	86.0	(37)	81.3	[33.2 – 174.0]
V_2 (L)	**871**	**(12)**	**873**	**[766 – 985]**
ω_{V_2} (CV%)	43.2	(29)	42.9	[27.6 – 61.6]
CL_S (L/h)	**193**	**(10)**	**192**	**[154 – 231]**
ω_{CL_S} (CV%)	32.9	(27)	31.3	[15.5 – 44.4]
$\theta_{Athletes}$	1.63	(21)	1.64	[1.23 – 2.16]
k_{13} (h^{-1})	**0.300**	**(16)**	**0.299**	**[0.233 – 0.390]**
$\omega_{k_{13}}$ (CV%)	41.2	(23)	40.6	[25.0 – 54.3]
CL_α (L/h)	**233**	**(22)**	**232**	**[177 – 293]**
k_{14} (h^{-1})	**0.000943**	**(22)**	**0.000951**	**[0.000751 – 0.00121]**
$\omega_{k_{14}}$ (CV%)	29.0	(41)	27.2	[18.5 – 36.6]
$\theta_{Athletes}$	2.91	(15)	2.91	[2.28 – 3.70]
k_{35} (h^{-1})	**0.0147**	**(22)**	**0.0149**	**[0.0124 – 0.0171]**
UR_PROD (L/h)	**0.079**	**(18)**	**0.080**	**[0.062 – 0.100]**
$\omega_{UR\_PROD_{SG-uncorrected}}$ (CV%)	73.2	(19)	71.8	[39.9 – 109.0]
$\sigma_{plasma\ salmeterol}$ (CV%)	21.5	(13)	21.5	[19.2 – 23.6]
$\sigma_{plasma\ \alpha-hydroxysalmeterol}$ (CV%)	38.1	(13)	38.0	[30.8 – 44.8]
Correlation σ_{plasma} (%)	51.6	(26)	52.0	[32.7 – 65.1]
$\sigma_{urine\ salmeterol\ (low)}$ (CV%)	29.1	(19)	29.2	[22.3 – 35.0]
$\sigma_{urine\ salmeterol\ (mid)}$ (CV%)	40.7	(21)	40.3	[35.8 – 45.9]
$\sigma_{urine\ \alpha-hydroxysalmeterol\ (mid)}$ (CV%)	37.9	(15)	37.9	[30.9 – 44.7]
$\sigma_{urine\ salmeterol\ (high)}$ (CV%)	56.7	(26)	56.5	[41.4 – 74.8]
$\sigma_{urine\ \alpha-hydroxysalmeterol\ (high)}$ (CV%)	51.4	(13)	50.7	[40.8 – 60.7]
Correlation $\sigma_{urine\ (Jessen\ et\ al.)}$ [4] (%)	60.7	(30)	60.0	[44.2 – 73.0]

$P_i = P \times \theta^{Athletes} \times e^{\eta_i}$ P: typical value of parameter (CL_S or k_{14}); Athletes (0;1).

D_1: intravenous-like bolus absorption; k_{10}: elimination rate constant for plasma salmeterol; CL_S: apparent clearance of plasma salmeterol; V_1 and V_2 : apparent central and peripheral volume of plasma salmeterol, respectively; Q: apparent intercompartmental clearance; k_{13}: plasma conversion of salmeterol into α-hydroxysalmeterol; V_3: apparent volume of plasma α-hydroxysalmeterol; k_{30}: elimination rate constant for plasma α-hydroxysalmeterol; CL_α: apparent clearance of plasma α-hydroxysalmeterol; k_{14} and k_{35} : urinary excretion rate constant of salmeterol and α-hydroxysalmeterol, respectively; V_4: urine volume of salmeterol; V_5: urine volume of α hydroxysalmeterol. UR_PROD: urine production; ω: between-subject variability; σ: proportional residual error combined together when found to be similar between studies (i.e., low, medium, and high variability).

Monte Carlo simulations of salmeterol in urine



Individual predictions of salmeterol in urine (corrected by the SG) after a one-week administration in athletes with bladder voiding every 4 hours. The solid white lines represent the median, while the dark surfaces encompass the 50% prediction intervals, and the light surfaces the 95% prediction intervals. The vertical dotted line represents a time after dose of 2h.

In a sample collected 2 hours post-dose, simulations accounting for both between-subject variability and residual errors show that the probability of detecting salmeterol urine concentrations above the MRL would be 0.2% after repetitive prohibited doses of 200 µg twice a day.

Conclusions

The current MRL for salmeterol in urine is not expected to detect salmeterol concentrations in urine at therapeutic doses. However, its expected sensitivity is low for cases of misuse/doping not involving massive overdosage.

LinkedIn

References

[1] World Anti-Doping Agency. The Prohibited List. https://www.wada-ama.org/en/prohibited-list#search-anchor. [2] World Anti-Doping Agency. WADA Technical Document - TD2022DL. 2022; [3] Jacobson GA, Hostrup M. *Drug Testing and Analysis.* 2022; [4] Jessen S, et al. *Drug Testing and Analysis.* 2021; [5] Jacobson GA, et al. *Drug Test Anal.* 2017; [6] Hostrup M, et al. *Journal of Sports Medicine & Doping Studies.* 2012; [7] Deventer K, et al. *Ther Drug Monit.* 2011.