HIGH AMOUNT OF SALBUTAMOL: A CASE REPORT

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Introduction

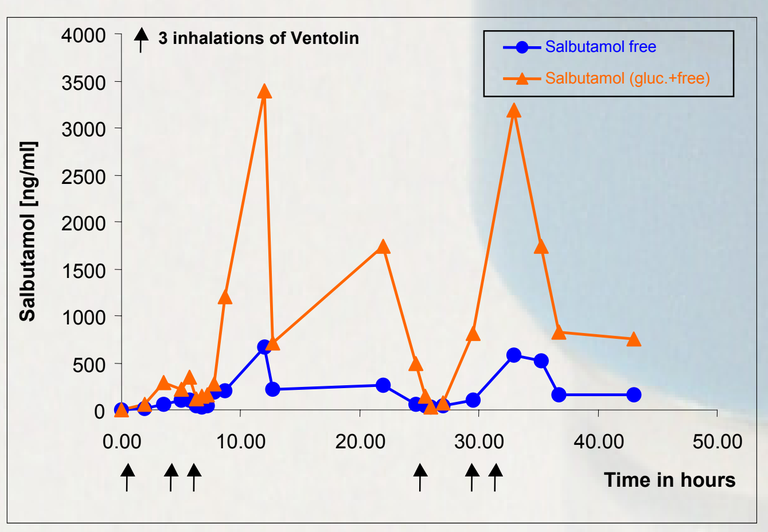
β-agonists as Salbutamol are forbidden in competition but they are authorized by inhalation with medical justification. Salbutamol measured in urine is considered as stimulant when the concentration is higher than 100 ng/ml and it is considered to have an anabolic effect when the concentration is higher than 1000 ng/ml. A few years ago some experiences made in our laboratory with healthy volunteers had shown that the concentrations as Salbutamol can be higher than 1000 ng/ml with therapeutic dose of Ventolin® nebulizer.

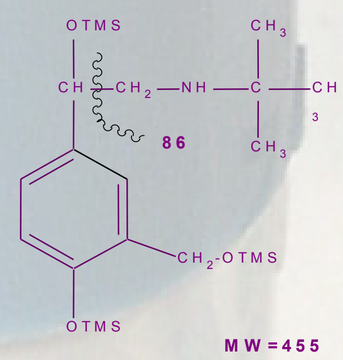
Recently, in an urine of an athlete in competition, high concentration of Salbutamol (about 8000 ng/ml) was detected. This athlete took regularly Ventolin® and corticoids (Symbicort) because he suffered from an allergic and effort asthma. The athlete said that he took Ventolin® only before training and competition especially in spring and summer. It was decided with the Swiss Medical Commission to perform some investigations with this athlete in order to reproduce the excretion of high concentration of Salbutamol.

Preparation of the sample and analysis

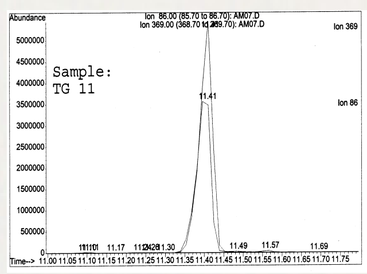
The free and glucuronide fractions were analysed.

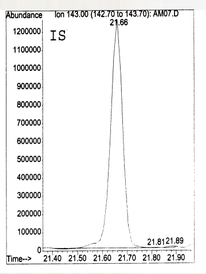
2.5 ml urine + IS (Methylandrostanediol)
Solid Phase extraction C18
Hydrolyse with E.Coli
Extraction with TBME
TMS derivatization

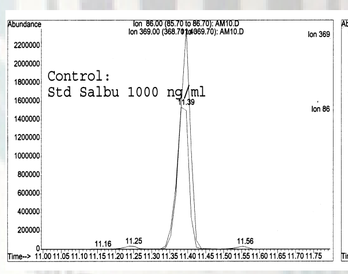


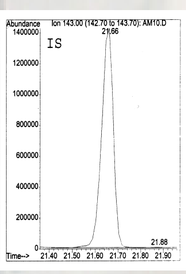


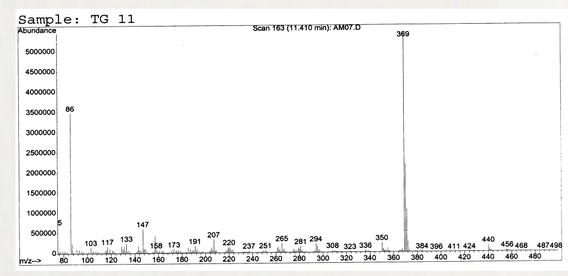
Urinary Salbutamol (free and glucuronide ng/ml) as a function of time

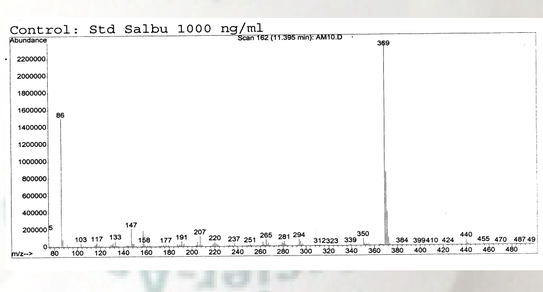












Chromatogramms and mass spectra of Salbutamol:
Left: Urine taken 12 hours after beginning of treatment; Right: Standard at 1000 ng/ml

Protocole of the study

One inhalation of Ventolin® = 0.1 mg of Salbutamol.
Days 2 and 3 the athlete had taken 3 x 3 inhalations/day.

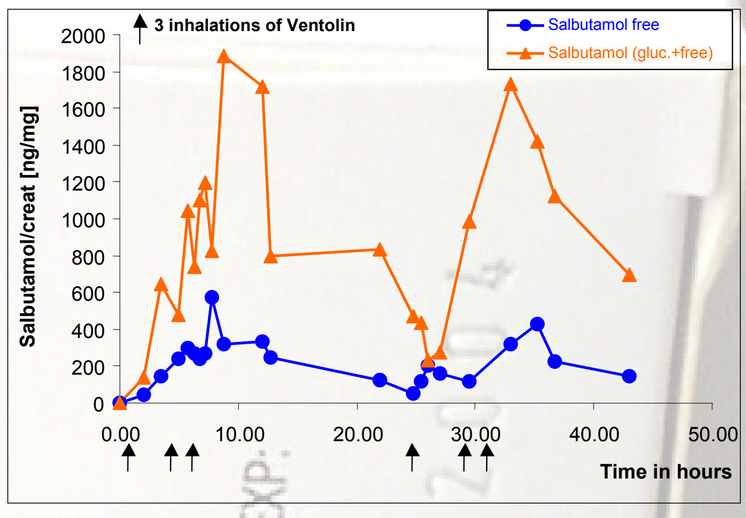
Day	1	2	3	4
Treatment (Ventolin®)	-	3 inhalations	3 inhalations	-
Time	-	12h / 16h / 17h	12h / 16h / 17h	-
Symbicort (corticoid)	-	-	+ (8h)	-
Urine collection	-	all urines	all urines	Morning urines

GC-MSD Analysis

The analysis were performed by Gas Chromatography-Mass Spectometry (Agilent 5973N) in SIM mode for quantification.

Results

- The day of the positive control the athlete took Ventolin ® about one hour before the race (3 inhalations) then 30 min before the race (3 inhalations) and 3 inhalations at the arrival and before the antidoping control.
- In the protocol the athlete was submitted, the Salbutamol dosage wasn't so high and could be considered as normal. The concentrations of urinary Salbutamol were lower than what was obtained during the competition but totally in accordance with the respective dosage.
- Some concentrations were above 1000 ng/ml in the non-sulphated fraction.



Urinary Salbutamol/Creatinine (ng/mg) as a function of time

Concentrations of Salbutamol and T/E ratio.

Samples	Time in hours	T/E	Creatinine [mg/ml]	Conc Salbu free [ng/ml]	Conc Salbu gluc. [ng/ml]	Salbu free/creat [ng/mg]	Salbu gluc./creat [ng/mg]
TG 1	0.00	0.9	0.53	0.00	0	0.00	0.00
TG 2	2.00	0.8	0.38	17.60	50.74	46.54	134.16
TG 3	3.50	0.9	0.44	63.85	287.16	143.81	646.84
TG 4	5.00	1.2	0.45	107.09	214.19	237.69	475.39
TG 5	5.75	1.3	0.33	99.45	345.98	299.40	1041.63
TG 6	6.25	1.4	0.15	41.10	111.83	271.67	739.13
TG 7	6.75	1.3	0.13	32.71	148.98	242.59	1104.78
TG 8	7.25	1.2	0.14	36.39	163.59	266.60	1198.46
TG 9	7.75	1.2	0.33	187.48	270.22	572.90	825.72
TG 10	8.75	1.2	0.64	202.71	**1206.04**	316.91	1885.47
TG 11	12.00	1.2	1.97	**661.61**	**3385.42**	335.86	1718.58
TG 12	12.75	1.2	0.89	221.80	710.52	247.97	794.32
TG 13	22.00	0.8	2.08	261.36	**1734.71**	125.45	832.65
TG 14	24.75	0.8	1.04	54.53	487.25	52.64	470.36
TG 15	25.50	0.7	0.32	37.81	140.37	116.72	433.31
TG 16	26.00	0.9	0.14	28.55	33.52	199.60	234.32
TG 17	27.00	1.0	0.27	42.94	73.81	158.28	272.06
TG 18	29.50	0.8	0.82	97.54	809.73	118.87	986.81
TG 19	33.00	0.8	1.83	**584.41**	**3181.80**	318.75	1735.42
TG 20	35.25	1.0	1.23	**526.10**	**1740.64**	428.87	1418.96
TG 21	36.75	1.0	0.73	163.76	821.71	223.79	1122.93
TG 22	43.00	0.8	1.07	152.29	748.38	142.05	698.05
Sample	*07.07.02*	*1.1*	*2.57*	*1318.98*	*8549.17*	**512.83**	**3324.00**

Conclusion

This experience showed that Salbutamol aerosol application in a therapeutic dosage (or close to) can lead to concentrations of non-sulphated Salbutamol in urine over 1000 ng/ml.

The concentration of non-sulphated Salbutamol was significantly higher to what was found during the protocol: this is certainly due to a more frequent intake of Ventolin® around the competition.

It should be detemined if this frequent intake of Ventolin® is compatible with the status of top athlete.

A warning against Salbutamol « abuse » in case of asthma therapy can be made to the athletes and the doctors.