Codeine influences the serum and urinary profile of endogenous androgens but does not interact with the excretion rate of administered testosterone

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Abstract

Today's doping tests involve longitudinal monitoring of urinary steroids including the testosterone glucuronide and epitestosterone glucuronide ratio (T/E) in an athlete biological passport (ABP). The aim of this study was to investigate the possible influence of short term use of codeine on the urinary excretion of androgen metabolites included in the steroidal module of the passport prior to and after the co-administration with testosterone.

The study was designed as an open study with the subjects being their own control. Fifteen healthy male volunteers received therapeutic doses of codeine (Kodein Meda) for 6 days. On day three, 500 mg or 125 mg of testosterone enanthate (Testoviron®-Depot) was administered. Spot urine samples were collected for 17 days, and blood samples were collected at baseline, 3, 6 and 14 days after codeine intake.

The circulatory concentration of total testosterone decreased significantly by 20 % after three days use of codeine ($p=0.0002$) and an atypical ABP result was noted in one of the subjects. On the other hand, the concomitant use of codeine and testosterone did not affect the elevated urinary T/E ratio. In 75 % of the individuals, the concentration of urinary morphine (a metabolite of codeine) was above the decision limit for morphine. One of the participants displayed a morphine/codeine ratio of 1.7 after codeine treatment, indicative of morphine abuse.

In conclusion our study shows that codeine interferes with the endogenous testosterone concentration. As a result, the urinary steroid profile may lead to atypical findings in the doping test.

Introduction

In order to detect doping with endogenous steroids, the athlete's urinary steroid profile is followed over time in the steroidal module of the athlete biological passport (ABP) [1]. This module monitors ratios of the urinary concentrations of testosterone (T), epitestosterone (E), androsterone (A), etiocholanolone (Etio), 5α- and 5β- androstan-3α,17β-diol (5α-diol and 5β-diol) [2]. These androgen metabolites are predominantly excreted as glucuronides, glucuronidated by UDP-glucuronosyl transferases, with (UGT) UGT2B17, 2B15 and 2B7 being the most essential isoforms [3 4 5 6].

Analgesic drugs such as codeine are widely used by athletes to treat various sport injuries. Codeine is not classified as a prohibited drug by World Anti-Doping Agency (WADA) [7]. Some of the codeine is bio-activated by CYP2D6 to the active metabolite morphine [8] which is further conjugated to the inactive morphine-3-glucuronide (M3G) and the more potent morphine-6-glucuronide (M6G). The major UGT involved in codeine and morphine conjugation is UGT2B7 [9]. Thus, it is possible that pharmacological doses of codeine may interact with androgen conjugation catalyzed by the same UGTs. Theoretically, codeine could interact with the ABP and hence also be used as a masking agent to hide the abuse of testosterone (and other androgens). It is also possible that the morphine/codeine ratio may be altered if codeine is co-administered with testosterone by a metabolic interaction.

It is known that opioid use may lead to androgen deficiency (reviewed by [10]) and a case-report show that already a few days opioid therapy suppresses the HPA axis [11]. Thus it is possible that codeine may interact with the circulatory levels of testosterone which may induce changes in the ABP. Given this situation, more knowledge on the disposition of androgen metabolites after codeine use is needed. As the pharmacokinetic interaction of codeine and testosterone has never been studied in vivo in man, our aim was to investigate the possible influence of short term use of codeine on the urinary excretion of androgen metabolites included in the steroidal module of the ABP prior to and after the co-administration with testosterone.

Material and Methods

Study population

Fifteen healthy male volunteers aged 18–45 years participated. No hormonal pharmaceutical compounds other than those in this study were allowed. For inclusion it was required that the subject was not a member of any organization belonging to the Swedish Sports Confederation. All participants gave informed consent consistent with the approval of the Ethics Review Board at Karolinska Institutet in Stockholm. The study (protocol number 2007-002655-16) was conducted according to the Helsinki declaration and the ICH Harmonized Tripartite Guideline for Good Clinical Practice.

The study was designed as an open study with subjects being their own controls. Three days before the study drugs were administered, morning urine samples were collected (baseline samples). On day 0 the participants received codeine (Kodein Meda-Meda AB) 50 mg × 3 times/day for six consecutive days.150 mg/day is within the recommended analgesic dose range (15-60 mg, 1-5 times/day) and often used for management of pain in sports [12]. After three days codeine treatment, an intramuscular injection of 500 mg (n=8) or 125 mg (n=7) testosterone enanthate (Testoviron®-Depot, Bayer) was administered by the study nurse. Samples of urine were further collected for 14 days, all between 06–10 am. All urine samples were stored at -20°C. Blood samples were collected on day 0 (prior to codeine intake), and 3, 6 and 14 days after codeine intake.

Urinary steroid profile and ABP-analysis

The steroid profile of the studied samples was analyzed in all eight subjects administered with 500 mg testosterone enanthate in order to see if codeine intake interacts with the urinary excretion profile after the administration of testosterone. Additionally, the steroid profile was studied in two of the subjects administered with 125 mg. These two were chosen since they displayed a major decrease in their circulatory testosterone levels.

For the steroid analysis we used a gas chromatography-tandem mass spectrometry (GC-MS/MS) method, accredited by WADA, as thoroughly described by Mullen et.al [13]. Briefly, the urinary steroid profile is analyzed with GC-MS/MS after a 2 mL sample aliquot has been subjected to hydrolysis with β-glucuronidase followed by liquid/liquid extraction using methyl *tert*-butyl ether and derivatization with N-Methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA).

The research version of the ABP was used to evaluate the longitudinal profiles of the urinary steroid data (Swiss Laboratory for Doping Analyses, Epalinges, Switzerland). Quantitative data of T, E, A, Etio, 5α-diol and 5β-diol as well as the specific gravity were entered into the program for each study subject and sample. The baseline samples correspond to samples 1-3. Samples 4-6 corresponds to codeine-only treatment, and the remaining samples are influenced by co-administration of codeine and testosterone. The threshold values calculated by the software on sample no. 3 (i.e., after three baseline samples) are considered the study

subject's true individual threshold. The thresholds calculated for samples 7–12 are influenced by the testosterone dose.

Urinary analysis of morphine and codeine

Codeine, morphine and their respective metabolites were analyzed simultaneously in all studied samples using direct injection on LC-MS/MS following a one-step sample dilution with internal standard solution.

Materials: The analyzed substances: codeine and the metabolite codeine-6β-D-glucuronide together with morphine and its metabolites morphine-6β-D-glucuronide and morphine-3β-D-glucuronide, the internal standards: Codeine-D3, morphine-D3 and morphine-3β-D-glucuronide-D3 were all purchased from Sigma Aldrich (Darmstadt, Germany). Water was produced locally using a Millipore (Darmstadt, Germany) Advantage A10 (18 MΩ resistance). Methanol, formic acid, were purchased from Fisher (Longborough, UK). Surine™ (negative urine control and used for calibrator samples) and ammonium formate were purchased from Sigma Aldrich (Darmstadt, Germany).

Sample preparation: The sample preparation was performed using dilution with internal standard solution: 100 µL of urine sample and 400 µL of internal standard solution. The internal standard solution consisted of Codeine-D3 (0.1 µg/mL), morphine-D3 (0.1 µg/mL) and morphine-3β-D-glucuronide-D3 (0.3 µg/mL) dissolved in mobile phase A. The calibrators used were prepared from six stocks of human urine, spiked at concentrations covering the range showed in table 2. The calibrators were prepared simultaneously with the same procedure as for the samples. Samples with higher concentration then covered in the validation and by calibrators were subsequently diluted with mobile phase A to be within the investigated linear range of the method.

LC-MS/MS: Separation was performed by an Acquity UHPLC system (Waters, Milford, MA, USA) on YMC-UltraHT Hydrosphere C18 column 100 × 2.0 mm with 2-µm particles with precolumn YMC- Hydrosphere C18 5 × 2.1 mm (YMC Co. Ltd, Kyoto, Japan). The mobile phases were 10 mM ammonium formate adjusted pH 4.4–4.6 (A) and 10 mM ammonium formate adjusted pH 4.4–4.6 in 90% MeOH (B). Injection volume was 5 µL. Separation was performed with a flow-rate at 0.4 mL/min and a column temperature at 50 °C by a linear gradient with initial composition at 5% B to 100% B at 4.0 min. The composition,

100% B, was held during 1.0 min and then decreased to 5% B at 5 min. Equilibration between injection was set to 1.5 min (total run time 6.5 min). The mass spectrometer was a Quattro Premiere with an electrospray interface (Micromass, UK). The capillary potential was set to 1 kV and the nitrogen desolvation and cone gas flow was 1000 L/hr and 50 L/hr, respectively. Capillary and Aux gas temperature was both set to 350 °C. The MS/MS transitions and the respective collision energies are showed in table 1.

Validation: The method was validated with the results showed in table 2. The validation included the limit of detection (LOD), limit of quantification (LOQ), repeatability, intermediate precision, linearity and the range.

Serum analysis

Testosterone, SHBG, LH and FSH were determined with accredited methods at the division of clinical chemistry, Karolinska University Laboratory. Total serum testosterone was measured using chemiluminescent technology UniCel® DxI 800 Immunoassay System and Access Testosterone Reagent Packs (Cat #33560) from Beckman Coulter (Brea, CA, USA). LH hormone and FSH were determined with an AutoDELFIA instrument and two-site immunoradiometric assays using kits (PN: B017-201 and B031-101) from PerkinElmer (PerkinElmer Life and Analytical Sciences, Turku, Finland).

UGT2B17 genotyping

DNA was extracted from whole blood samples using QIAamp® DNA Blood Mini kit from Qiagen (Hilden, Germany). DNA-samples were used to genotype for the UGT2B17 deletion polymorphism as we have previously described [4]

Results

Validation of LC-MS method

The method was briefly validated with investigations of LOD/LOQ, repeatability and intermediate precision followed by a linearity study of the working range of the method. The

results are presented in table 2. It was shown that the method was able to give reliable measurements of codeine/morphine and metabolites in urine.

Serum hormone levels after 3 days codeine administration

Total testosterone concentrations were analyzed prior to and after three days codeine intake at a therapeutic dose (50 mg, 3 times/day). On average the serum levels of total testosterone were decreased by 20 % after three days of codeine from a median total testosterone concentration of 15 nmol/L (range 10-23 nmol/L) to 12 nmol/L (range 4.3-20 nmol/L, p=0.0002) (figure 1a). The concentrations of gonadotropins and SHBG did not change after 3 days codeine intake (figure 1b, 1c, 1d).

Serum hormone levels after co-administration with testosterone

After testosterone administration, the testosterone serum levels increased, whereas LH and FSH decreased. The increase in testosterone concentration after 500 and 125 mg testosterone were 3 and 2-fold respectively ($p<0.0001$ and $p=0.02$). Administration of the higher dose yielded testosterone concentrations above the detection limit (>50 nmol/L) in all subjects. FSH decreased 40 % ($p=0.09$) and 50 % ($p=0.06$), and LH decreased 60 % ($p=0.06$) and 76 % ($p=<0.0001$) six days after administration of 125 and 500 mg testosterone, respectively. The SHBG concentration was not affected by testosterone administration (data not shown).

Urinary concentration of steroid metabolites after the co-administration of codeine and 500 mg testosterone

All the metabolites included in the ABP were analyzed in samples obtained from the subjects administered with 500 mg testosterone enanthate. The excretion rates of the metabolites were not influenced by the intake of codeine. The urinary concentrations of the three samples collected prior to codeine intake (-2, -1, 0) did not differ compared to the concentrations observed on day 3 i.e. after 3 days intake of therapeutic doses of codeine. As expected, injection of 500 mg testosterone enanthate resulted in an increase of all the metabolites except for epitestosterone concentrations which decreased (figure 2). Median Cmax post 500

mg testosterone were 236, 8048, 5283, 329, 644 ng/mL for testosterone, Andro, Etio, 5α-diol, and 5α-diol, respectively.

The AUC of the T/E ratio when testosterone was co-administered with codeine was compared with the corresponding AUC from our previous study of 500 mg testosterone administered alone [14]. The AUC of the T/E ratio of the subjects are shown in figure 3. One of the participants was identified as homozygous for UGT2B17 del/del and was excluded. No differences in the AUC were noted when testosterone was administered alone (median 202 range 87-301) as compared to when administered during co-use of codeine (median 165 range 135-279) in UGT2B17 carriers. Two of the volunteers participated in both of the studies and the intra-individual variation appears to be smaller than the inter-individual variation.

Intra-individual variation and ABP-analysis

The three baseline values obtained before any study drugs were administered were added to the ABP followed by the values after codeine intake. One of the 10 individual passports was identified as atypical for the T/E ratio (figure 4). The other ABP-ratios were not affected. In the other 9 participants, all the ratios were within the individual reference ranges (data not shown).

When the values after testosterone injection were added together with three baseline values and three codeine values, all individuals were identified as atypical finding regardless of testosterone dose. Thus, the administration of testosterone (500 or 125 mg) was not concealed by codeine intake, as illustrated by figure 4b.

Urinary concentrations of codeine and morphine prior to and after testosterone administration

The urinary concentrations of morphine and codeine as well as the glucuronide metabolites M6G, M3G and C6G were not affected by testosterone injection (table 3). There were large inter-individual variation in the concentration of total codeine (CV 76%) and morphine (CV

93 %) excreted. One of the subjects displayed no concentrations of morphine and M6G, and very low concentration of M3G (<70 ng/mL) at all times during codeine treatment.

Two and four days after the last intake of codeine, urinary codeine metabolites were found in four and three of the subjects, respectively. Morphine was detected only in one of the subjects post the codeine dose, and hence the (morphine+M3G+M6G)/(codeine+C6G) ratio in this individual increased from 0.06 (Cmax during treatment) to 0.28 and 1.71 two and four days after the last dose. Six days after codeine treatment no codeine and morphine metabolites were detected in any of the subjects.

Discussion

Here it was studied if codeine pretreatment alters the urinary profile of endogenous steroid metabolites prior to and after the administration of 125 and 500 mg testosterone enanthate. One of the subjects was identified with an atypical ABP finding after three days use of codeine when 3 baselines were added into the ABP. The increase in T/E ratio appears to be a result of a more profound decline in epitestosterone compared to testosterone. This is, to our knowledge, the first time it is shown that short term use of codeine may confound the urinary steroid profile.

It was found that only three days use of codeine is associated with a major decrease of serum testosterone in some individuals confirming the finding described in a case report [11]. This is consistent with the fact that long term use of opioids, particularly high doses of morphine, methadone and heroin, may lead to hypogonadism [15 16 17 18]. Opioids have been shown to interfere with GnRH secretion from the hypothalamus resulting in decreased LH and FSH as reviewed by [10]. However, since LH and FSH were not coordinately decreased after 3 days codeine treatment different mechanisms may be involved. Several steroid hydroxylation pathways are markedly down-regulated in rats after morphine treatment [19]. In all probability, this down-regulation of enzymes generating precursors of testosterone has a human correlate and may contribute to the decrease of testosterone concentrations in serum observed by us. There are also data to suggest that non-opioid receptor mediated mechanisms may operate

since morphine and pethidine had completely different effects on the activity of different CYP enzymes in rats [20]. It is also possible that opioids may exhibit a direct effect on the testes as have been seen in some methadone users [17].

Some athletes may be using lower doses of codeine than used herein[12] and it would be interesting to perform a dose-relation study in order to identify the lowest dose that influences the testosterone levels. Moreover it may be of interest to study other opioids. Both animal and human studies indicate that different opioids exert varying effects on testosterone levels [21 22]. Future studies are warranted to study if a short-term use of other opioids i.e. tramadol affect the serum levels of testosterone and the urinary profile of the ABP-ratios. It would also be of interest to study the impact of codeine on serum and urinary steroid profile in females. In females most of the testosterone is generated from adrenal dehydroepiandrosterone sulfate (DHEAS), whereas in males substantial amounts of testosterone is produced from the testis [23 24] and hence the systemic effects could be different. Moreover, gender specific pharmacokinetic differences in opioid metabolism have been noted [25].

An increase in the urinary T/E ratio may be a result of testosterone increase as well as epitestosterone decrease. In the three subjects with the most profound effects on the serum testosterone levels, a decrease in all the urine metabolites was observed. Epitestosterone was more suppressed than testosterone in one of them, leading to an increase in T/E ratio. Generally, urinary epitestosterone excretion seems to be more affected by hormonal serum fluctuations than other androgen metabolites. The use of hormonal contraceptives, different phases of the menstrual cycle and pregnancy are examples of conditions that have an impact on the circulatory hormone levels [26] and associated with a larger impact on urinary epitestosterone than testosterone concentration in females [27 13 28].

The administration of testosterone leads to a dose related influence on the circulatory levels of testosterone in line with our previous dose study [29]. The urinary excretion rate of the androgen metabolites and the ABP outcome is in agreement with our previous results [14] i.e. that the steroid passports in all individuals, including UGT2B17 *del/del*, would be flagged as

atypical if three baseline values have been added in the passport for both doses investigated. Co-administration of codeine did not affect the outcome of the results. Our results indicate that codeine could not conceal the administration of testosterone, at least not the administration routes and doses used here. However, as only one of the study participants was identified as UGT2B17 *del/del* we cannot draw any conclusion if this is also true in subjects homozygous for the UGT2B17 deletion.

A methodological limitation with this study is that the serum concentrations of testosterone were analyzed with an immunoassay. It is well recognized that LC-MS/MS is more specific since immunoassays may overestimate concentrations due to cross-reactivates, particularly in pediatric and female populations [30]. Also ethnicity in females may be associated with lack of specificity using RIA [31]. However, in male adults it seems to be a strong correlation between RIA and LC-MS/MS results [32] indicating that RIA may be a reliable method for testosterone measurements for our baseline samples (prior to testosterone administration). Nevertheless it is possible that an even more profound decrease in testosterone would have been seen with an LC-MS/MS approach and it would also have been possible to monitor the total increase in testosterone after the administration of the highest dose of testosterone enanthte.

Morphine is on the WADA prohibited list, whereas the use of codeine is accepted. Since codeine is activated by CYP2D6 to morphine, codeine use will lead to the formation of morphine, however most often at much lower concentrations than those found during therapeutic use of morphine. Therefore WADA has stipulated a threshold at 1.0 µg/mL, and a decision limit at 1.3 µg/mL which is the cut-off value for morphine, implicating that higher concentrations should be reported as adverse analytical finding (AAF) with a "comment" if codeine is also present [33]. This cut-off value was exceeded in 75 % of the participants during codeine treatment, but the morphine/codeine ratio was low indicating that codeine rather than morphine was causative.

The (morphine+M3G+M6G)/(codeine+C6G) ratio is often used in forensic medicine to discriminate if an individual has used codeine or morphine, and a ratio above 1 is indicative of morphine use [34 35 36]. Four days after the codeine treatment, one of the participants showed a morphine+M3G+M6G)/(codeine+C6G) ratio of 1.71. Both codeine and morphine

metabolites were present at this time point as opposed to the other participants where no or only codeine metabolites were detected. The reason for the long persistence of morphine may be due to high activity of CYP2D6. Similarly, a high morphine/codeine ratio have been found in serum in CYPD6 ultrarapid and extensive metabolizers 24 hours after a single dose of 30 mg codeine [37].

The CYP2D6 phenotype is highly dependent on a gene deletion polymorphism as well as several functional SNPs [38]. If CYP2D6 genotype information is to be used for pharmacokinetic guidance, different scoring systems for CYP2D6 genotype-predicted activity have been presented [38 39]. Nevertheless, still some CYP2D6 phenotypes may be misclassified as "wild type" due to rare polymorphisms. Moreover, genetic variation in other genes, i.e. UGT2B7 may also affect the metabolism of morphine [40,41].

In conclusion it was found that three day´s codeine treatment decreases the circulatory levels of testosterone. Codeine may also interfere with the urinary steroid profile, which should be taken into consideration when evaluating steroid passports. Moreover, after a six days codeine treatment, the excretion rate of morphine and codeine metabolites may lead to high morphine/codeine ratios in some individuals.

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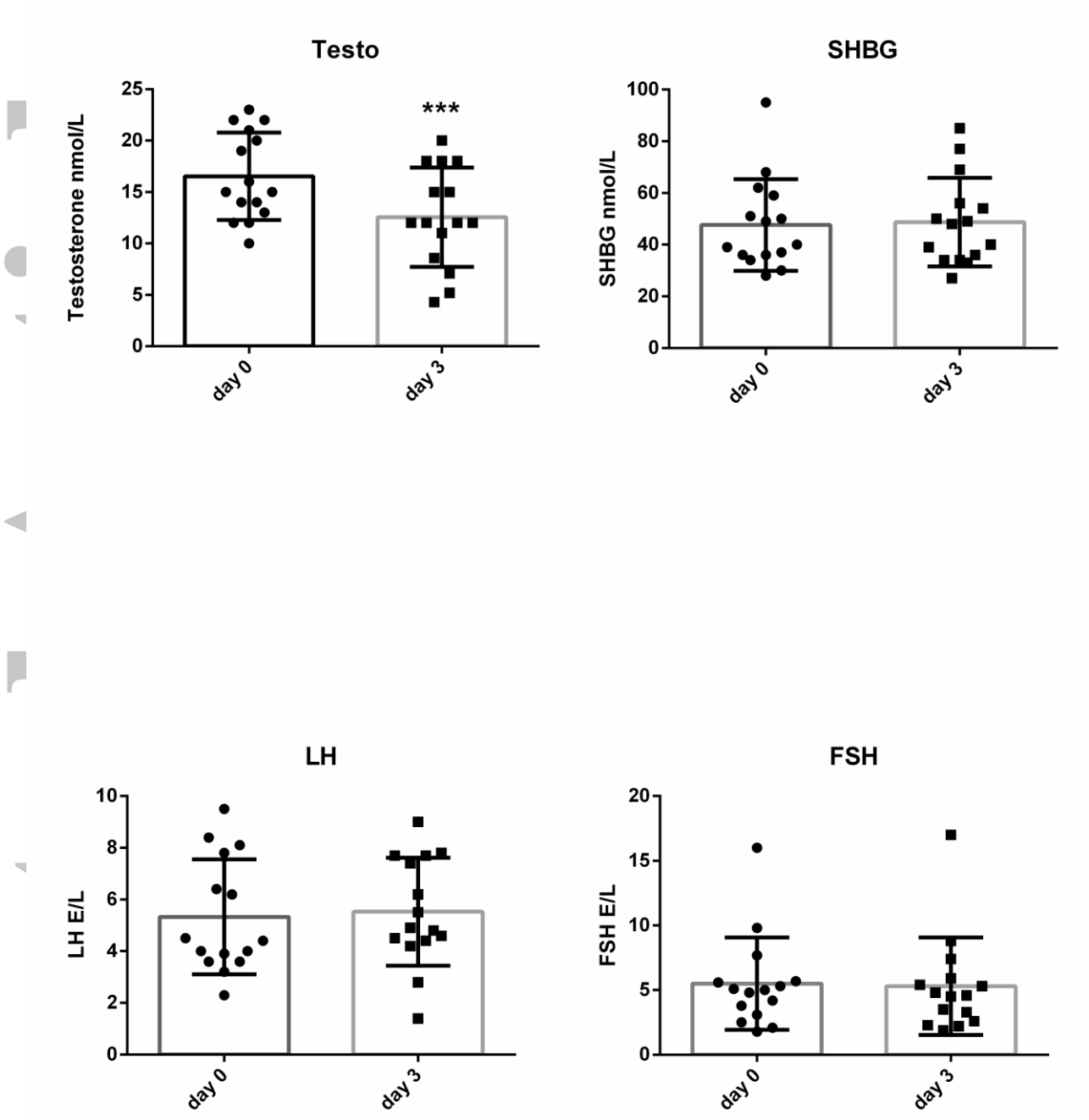


Figure 1. Serum concentrations of total testosterone, SHBG, LH and FSH prior to and 3 days after therapeutic codeine use (50mg*3/day). Total testosterone concentration was decreased after 3 days codeine use, whereas SHBG, LH and FSH were unaffected.

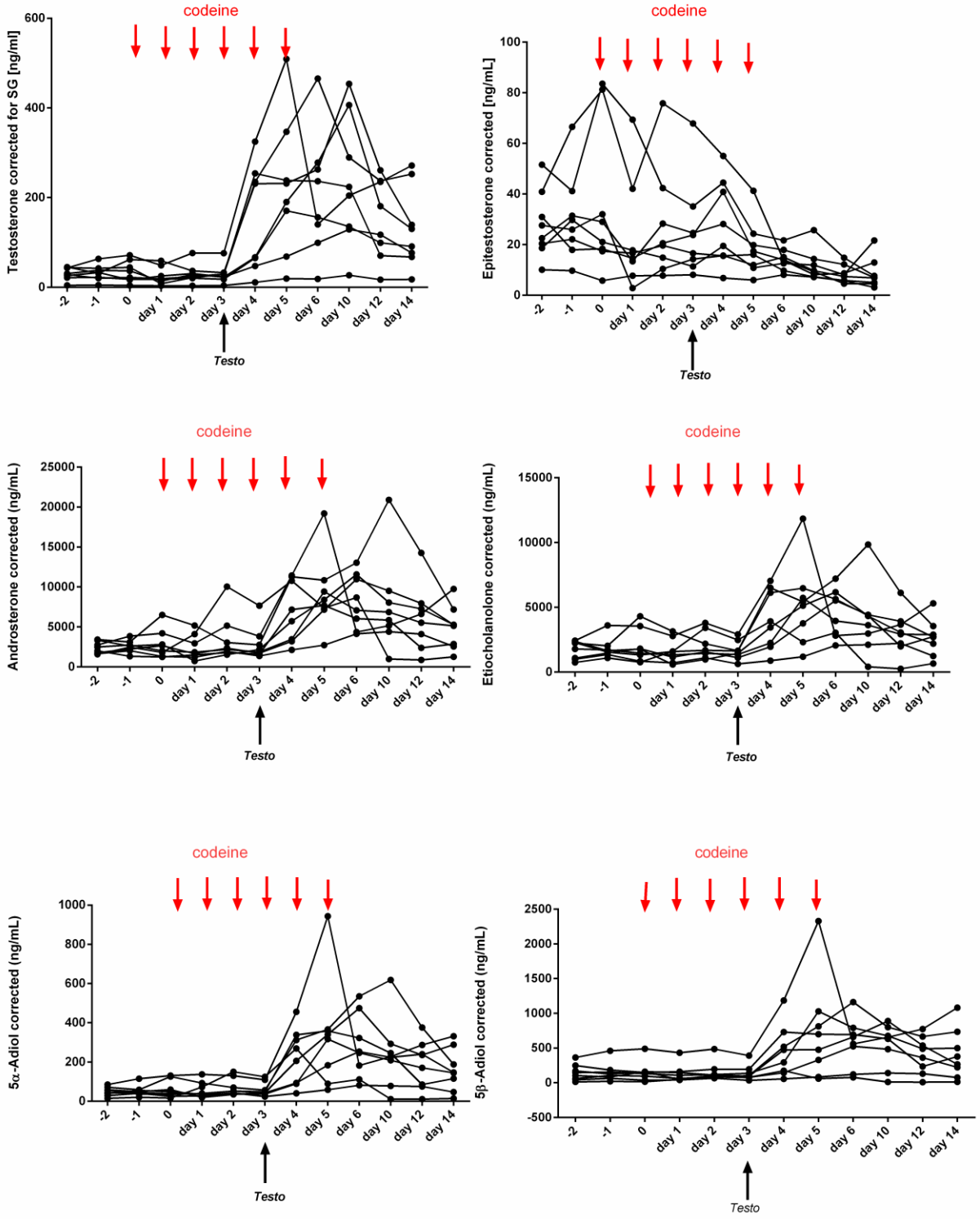


Figure 2. Androgen metabolites prior to, during and after 6-days codeine treatment (n=8). On day 3, 500 mg testosterone enanthate was administered.

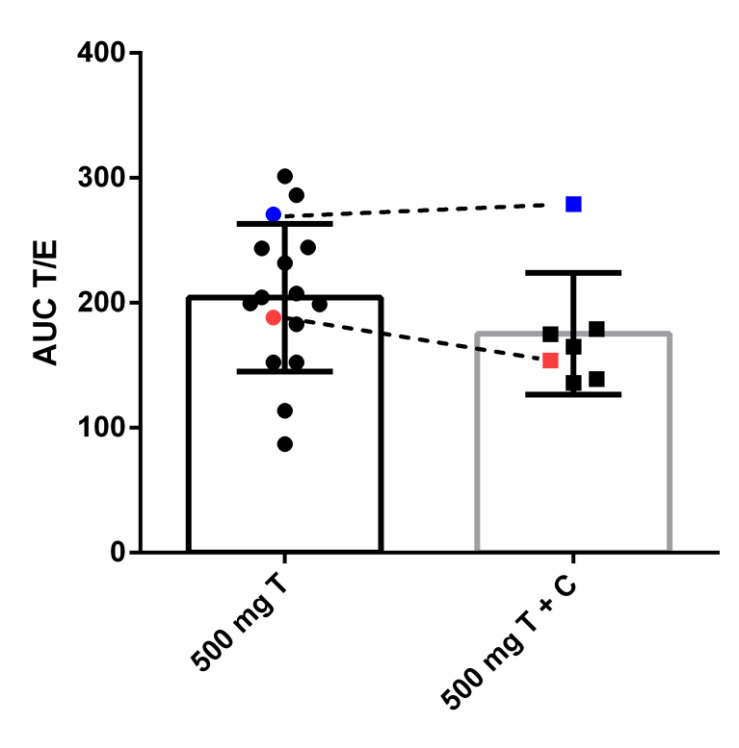
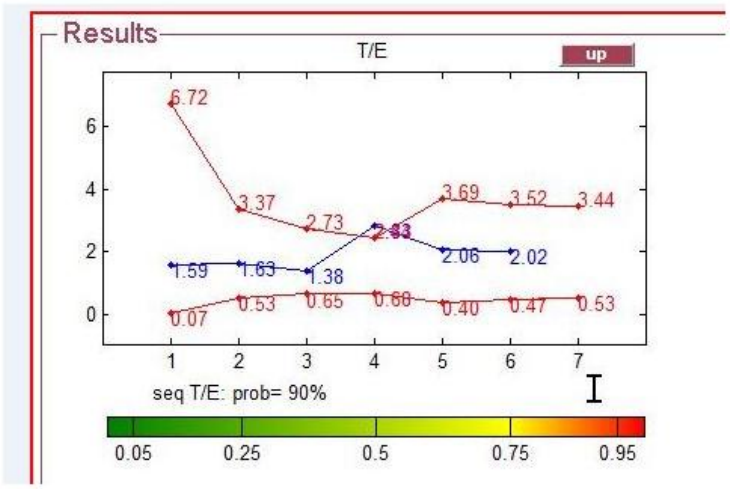


Figure 3. Urinary AUC of T/E-ratio in UGT2B17 positive men administered with 500 mg testosterone (T) alone and after a three days codeine treatment (T+C). The 3-days pretreatment were followed by another 3 days of codeine treatment. The AUC after co-administration of codeine and testosterone was not different as compared to testosterone alone. Two of the subjects participated in both the studies as illustrated by dotted lines.

A)



B)

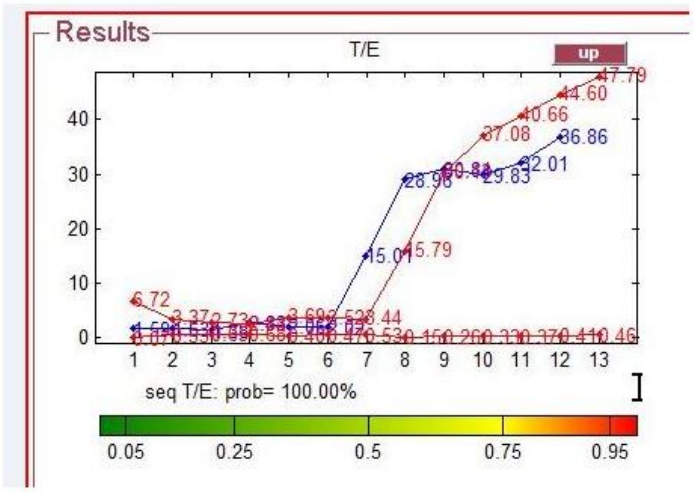


Figure 4. ABP-profiles during A) codeine treatment and B) after 500 mg testosterone. The first three T/E values were baseline values followed by three T/E values obtained during codeine treatment. A) Already after one day (3 doses of codeine) the T/E ratio was above the individual threshold. B) After receiving 500 mg testosterone on day 6 the T/E ratio increased profoundly.

Table 1. SRM transitions used during the LC-MS/MS analysis. Quantifier in bold.

Substance	Transition (CE) m/z (eV)
Morphine	**286.3 - > 165 (38)**, 286.3 - > 152.9 (56), 286.3 - > 201 (30)
Morphine-D3	**289.3 - > 165 (36)**
Morphine-6β-D-G	**462.3 - > 286.3 (30)**, 462.3 - > 165 (50)
Morphine-3β-D-G	**462.3 - > 286.3 (30)**, 462.3 - > 165 (50)
Morphine-3β-D-G-D3	**465.3 - > 289.3 (35)**
Codeine	**300.3 - > 165 (36)**, 300.3 - > 183 (28)
Codeine-D3	**300.3 - > 152 (69)**
Codeine-6β-D-G	**476.4 - > 300.3 (54)**, 476.4 - > 193.2 (28)

Table 2. Validation data for the LC-MS/MS method.

Substance (spiked concentration for precision samples µg/mL)	LOD (µg/mL)	LOQ (µg/mL)	Repeatability n=6 (%RSD, SD µg/mL, Average µg/mL, spiked concentration µg/mL)	Intermediate precision n=5 (%RSD, SD µg/mL, Average µg/mL)	Linearity R^2	Investigated Linearity range (µg/mL)
Morphine (0.02)	0.001	0.01	16, 0.00648, 0.0395	15, 0.00689, 0.0454	0.998	0.1-1.1
Morphine-6G (0.1)	0.002	0.1	5.5, 0.0119, 0.216	6.4, 0.0142, 0.223	0.997	0.1-1.1
Morphine-3G (2)	0.002	0.1	4.1, 0.0538, 1.31	4.8, 0.0598, 1.25	0.992	0.5-8
Codeine (0.2)	0.003	0.1	8.4, 0.0174, 0.207	N/A	0.995	0.1-80
Codeine-6G (16)	0.008	5	4.8, 0.784, 16.4	N/A	0.998	5-80

Table 3. Urinary concentrations of total morphine and codeine, and the glucuronidated metabolites during six days codeine treatment (3*50 mg/day). After day 3, an intramuscular administration of 500 mg testosterone enanthate was administered. Data are given as median (µg/mL) and range.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Morphine-6G µg/mL	0.50 (0-1.24)	0.57 (0-2.36)	0.64 (0-1.82)	0.68 (0-1.12)	0.57 (0-1.57)	0.48 (0-1.60)
Morphine-3G µg/mL	2.21 (0.02-3.91)	2.35 (0.05-6.59)	2.44 (0.05-6.68)	1.85 (0.04-4.57)	2.32 (0.07-5.28)	2.18 (0.04-4.20)
Codeine-6G µg/mL	56.22 (36.53-124.1)	109.86 (26.31-251.99)	95.79 (37.61-179.80)	71.63 (15.36-135.39)	106.75 (45.59-194.80)	54.875 (29.28-202.38)
Total Morphine µg/mL	1.74 (0.013-2.54)	1.77 (0.031-5.57)	1.78 (0.036-5.302)	1.62 (0.024-3.54)	2.20 (0.044-4.90)	1.67 (0.027-3.56)
Total Codeine µg/mL	36.72 (23.23-79.52)	42.89 (17.66-159.65)	51.45 (25.25-114.11)	45.67 (10.28-85.75)	84.81 (29.35-142.66)	41.75 (19.23-128.89)
M+M6G+3G/ C+C6G	0.031 (0.0005-0.099)	0.027 (0.0007-0.055)	0.034 (0.001-0.083)	0.036 (0.0007-0.160)	0.028 (0.0007-0.086)	0035 (0.001-0.063

Title:

Codeine influences the serum and urinary profile of endogenous androgens but does not interact with the excretion rate of administered testosterone

Authors:

Lehtihet M, Andersson A, Börjesson A, Schulze J, Rane A, Ericsson M, Ekström L*

Key findings:

Three days intake of codeine decrease serum levels of total testosterone

Co-use of codeine and testosterone do not interact with each other

Codeine use may be a confounder when interpreting the athlete biological passport