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Research of stimulants and anabolic steroids in dietary supplements

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The purpose of this study was to analyze the composition of 103 dietary supplements bought on the internet. The supplements were dispatched in four different categories according to their announced contents [creatine, prohormones, "mental enhancers" and branched chain amino acids (BCAA)]. All the supplements were screened for the presence of stimulants and main anabolic steroids parent compounds. At the same time, the research was focused on the precursors and metabolites of testosterone and nandrolone.

The study pointed out three products containing an anabolic steroid, metandienone, in a very high amount. The ingestion of such products induced a high quantity of metandienone metabolites in urines that would be considered as a positive antidoping test. The results have also shown that one creatine product and three "mental enhancers" contained traces of hormones or prohormones not claimed on the labels and 14 prohormone products contained substances other than those indicated by the manufacturer. The oral intake of the creatine product revealed the presence of the two main nandrolone metabolites (19-norandrosterone and 19-noretiocholanolone) in urine.

In the last few years, dietary supplements have been widely used by elite athletes who believe that products like creatine, prohormones, amino acids and "mental enhancers" would boost their physical and psychological abilities (Ekblom, 1996; Engelhardt et al., 1998; Appelgate, 1999; Di Luigi et al., 1999; Terjung, 2000; van Gammeren et al., 2001; Ziegenfuss et al., 2002; Sundgot-Borgen et al., 2003). Although a meta-analysis of available literature has recently demonstrated ergogenic effects of creatine and HMB (Nissen & Sharp, 2003), the beneficial effects of most of these products are not clearly established even if many studies have been carried out in this field (King et al., 1999; Leder et al., 2000; Graham, 2001; Lawrence & Kirby, 2002; Powers, 2002; van Gammeren et al., 2002). The widespread accessibility is also the cause of the expansion of the use of dietary supplements. Indeed, the industry specialized in supplement manufacture generates annual seals estimated at US $12 billion in 1999 (Pipe & Ayotte, 2002).

At the same time, positive cases appeared with very small urinary concentrations of forbidden substances like 19-norandrosterone. All these reasons drove some antidoping laboratories to investigate the real composition of the over-the-counter (OTC) supplements available on the internet, in shops or in fitness clubs (Geyer et al., 2000; De Cock et al., 2001; Green et al., 2001; Kamber et al., 2001). Many of these investigations pointed out that both hormonal and non-hormonal dietary supplements are mislabelled and may contain anabolic androgenic steroids or prohormones that could be metabolized to compounds that are produced by the metabolism of banned anabolic steroids like 19-nortestosterone (nandrolone) (Uralets & Gillette, 1999; Catlin et al., 2000; Ayotte et al., 2001; Colker et al., 2001; Geyer et al., 2001). It has also been demonstrated that some supplements may be contaminated with other substances like stimulants (caffeine, which is no more present on the World Anti-Doping Agency (WADA) prohibited list from 2004 and ephedrine) (Gurley et al., 2000).

Therefore, there is an evident risk for unintentional doping among the dietary supplement users. This danger is not well understood by the athletes and a regular education of athletes, coaches and medical staff would be necessary to decrease the abuse of the dietary supplements and its related risks.

In 2000, the Swiss Antidoping Laboratory and the Swiss Federal Office of Sports performed a first study on the dietary supplements. From the obtained results, athletes were informed about the findings

and warned of products bought from unknown sources. With this new study, the authors first wanted to know whether the situation has improved (or worsened) on the market and second to focus on products that are widely used and easily accessible in Switzerland. In our country, most people who consume dietary supplements buy the products through different internet sites. Indeed, not all the products are accessible at the markets or in drugstores. Therefore, the aim of this study was to check the real compositions of 103 OTC dietary supplements. The selection of the supplements was carried out randomly, except for the few Swiss manufacturers products, which were the most popular among the athletes. We screened the supplements for contaminations with major anabolic steroid parent compounds, stimulants and traces of testosterone, nandrolone and their precursors.

Material and methods

One hundred and three products were ordered at the end of 2002 on different web sites. These products were classified into the following four categories: 37 supplements in the prohormones category, 42 creatine, 12 "mental enhancers" and 12 branched chain amino acids (BCAAs). It has to be noted that prohormones are banned by the International Olympic Council (IOC)/WADA, either directly by name or under the umbrella of being a substance related to anabolic–androgenic steroids. At present, this is not the case for the other three categories.

Extraction procedure and analyses for stimulants trace detection

One gram of the dietary supplement or 1 cap was dissolved in 5 mL methanol. The mix was shaken automatically for 10 min and centrifuged for 5 min at 2500 r.p.m. Five hundred microliters of methanolic layer was transferred to another glass tube, a drop of HCl 1% EtOH was added and the liquid solution was evaporated to dryness. The same procedure was carried out with 50 μL of the two standard mix.

Twenty-five microliters of diphenylamine (1 mg/mL, internal standard), 0.5 mL KOH 5N, 1 spatula of NaCl and 2 mL tert-Butylmethylether (TBME) were added and the mixture obtained was shaken mechanically for 10 min and centrifuged for 5 min at 2500 r.p.m. The organic phase was transferred in another tube and 1 spatula of Na_2SO_4 anhydrous was added. The mix was stirred manually with a vortex and the liquid part was removed in a 2 mL vial. Before closing the vial, a drop of H_2SO_4 was added.

The mass spectrometric (MS) detector used was a 5973 coupled to a 5890 gas chromatography (GC) and a 7873 injector acquired from Agilent (Palo Alto, California, USA).

The analyses were performed with a ZB-5 column (30 m, 0.25 mm, 0.25 μm, Zebron, Phenomenex, Torrance, CA, USA). The injection port was maintained at 200 °C and oven conditions started at 40 °C with an initial time of 1 min. The ramp consisted of 20 °C/min up to 310 °C and the final time was 3 min. The transfer line was maintained at 200 °C. All injections were administered in splitless mode and the acquisition was carried out in a scan mode between 40 and 450m/z.

Extraction procedure and analyses for testosterone and nandrolone (precursors and metabolites) trace detection

The extractions were performed according to the procedure described by Geyer et al. (2000) with some modifications. For the creatine, BCAA and the "mental enhancers" categories, 1 g (powder) of the dietary supplement or 1 cap was dissolved in 5 mL methanol and 40 μL of a 10 μg/mL methyl-testosterone solution were added as internal standard. The same procedure was carried out with the prohormones but in order to decrease the chromatographic signal 0.1 g was first dissolved in 5 mL methanol. After that, a dilution was made dissolving 10 μL of this solution in 5 mL methanol.

The mix was shaken automatically for 10 min and centrifuged for 5 min at 2500 r.p.m. Five hundred microliters of methanolic layer was transferred to another glass tube and evaporated to dryness. Five milliliters of KOH 0.1 M and 5 mL n-pentane were added. The mixture was then shaken mechanically for 10 min and centrifuged for 5 min at 2500 r.p.m. The n-pentane layer was transferred to another glass tube and 2 mL MeOH 95% (v/v) was added. The mix was shaken mechanically 10 min and centrifuged for 5 min at 2500 r.p.m. The n-pentane layer was discarded and the methanolic residue was evaporated to dryness. Fifty microliters of MSTFA/NH_4I/EtOH (1000/2/3; v/w/v) was added and the solution was heated for 20 min at 60 °C. The derivatized solution was transferred in a microvial and 1 μL was injected into GC–MS.

The MS detector used was a 5971 coupled to a 5890 GC and a 7873 injector acquired from Agilent.

All analyses were performed with a DB-XLB column (15 m, 0.25 mm, 0.25 μm, J&W Scientific, Folsom, CA, USA). The injection port was maintained at 280 °C and oven conditions started at 150 °C with an initial time of 1 min. The ramp consisted of 10 °C/min to 270 °C. All injections were splitless. The transfer line was maintained at 310 °C.

The analyses were performed in a single ion-monitoring mode. Table 1 shows the ions chosen for each potential steroid contaminant researched in this study.

Two different standard solutions containing the 11 researched steroids were extracted. The first solution contained testosterone, 5-norandrostenediol, 4-androstenediol, 5-androstenedione and 19-norandrostenedione, whereas the second solution enclosed androstenedione, nandrolone, Dehydroepiaudrosterone (DHEA), 4-norandrostenediol, 5-norandrostenedione and androstenediol. These substances were chosen in reference to Geyer et al. (2001). The above substances were selected because of their relation with the two major focused anabolic steroids. Figure 1(a) shows the prohormones and the metabolism of the nandrolone and Fig. 1(b) shows only the prohormones of the testosterone.

Analyses for other parent steroids detection

The extraction and the instruments used were the same as mentioned for the testosterone and nandrolone detection.

The analyses were performed in scan mode (m/z from 50 to 650). The ramp consisted of 10 °C/min to 270 °C with a final time of 3 min. All injections were performed in a splitless mode. Table 1 illustrates the compounds and the ions that were investigated.

Quantification of the detected contaminants

A macro programmation allowed the rapid detection of all the researched substances (steroids and stimulants, Fig. 2). The

Table 1. Parent compounds, testosterone, nandrolone and associated compounds with the related ions analysed in SIM mode by GC–MS.

Substance	*m/z*	Substance	*m/z*
4-Androstenediol*	405, 419, 434	Fluoxymesterone†	552, 462
4-Norandrostenediol*	240, 330, 420	Mesterolone†	157, 141
5-Androstenedione*	209, 234, 430	Metandienone†	444, 339
5-Norandrostenedione*	401, 416	Metenolone†	416, 195
5-Norandrostenediol*	225, 240, 330	Methyltestosterone†	446, 301
19-Norandrostenedione*	416, 194	Nandrolone*	194, 403, 418
Androstenediol*	344, 419, 434	Norethandrolone†	446, 287
Androstenedione*	415, 430	Oxandrolone†	363, 308
Bolasterone†	460, 445	Oxymesterone†	534, 389
Boldenone†	430, 206	Oxymetholone†	490, 475
Clostebol†	436, 401	Stanozolol†	472, 457
DHEA*	327, 417, 432	Testosterone*	417, 432
DHT*	434, 405	Testosterone propionate†	416, 401
Drostanolone†	432, 389	Turinabol†	478, 240

*Substances related to testosterone and nandrolone.

†Steroid parent compounds.

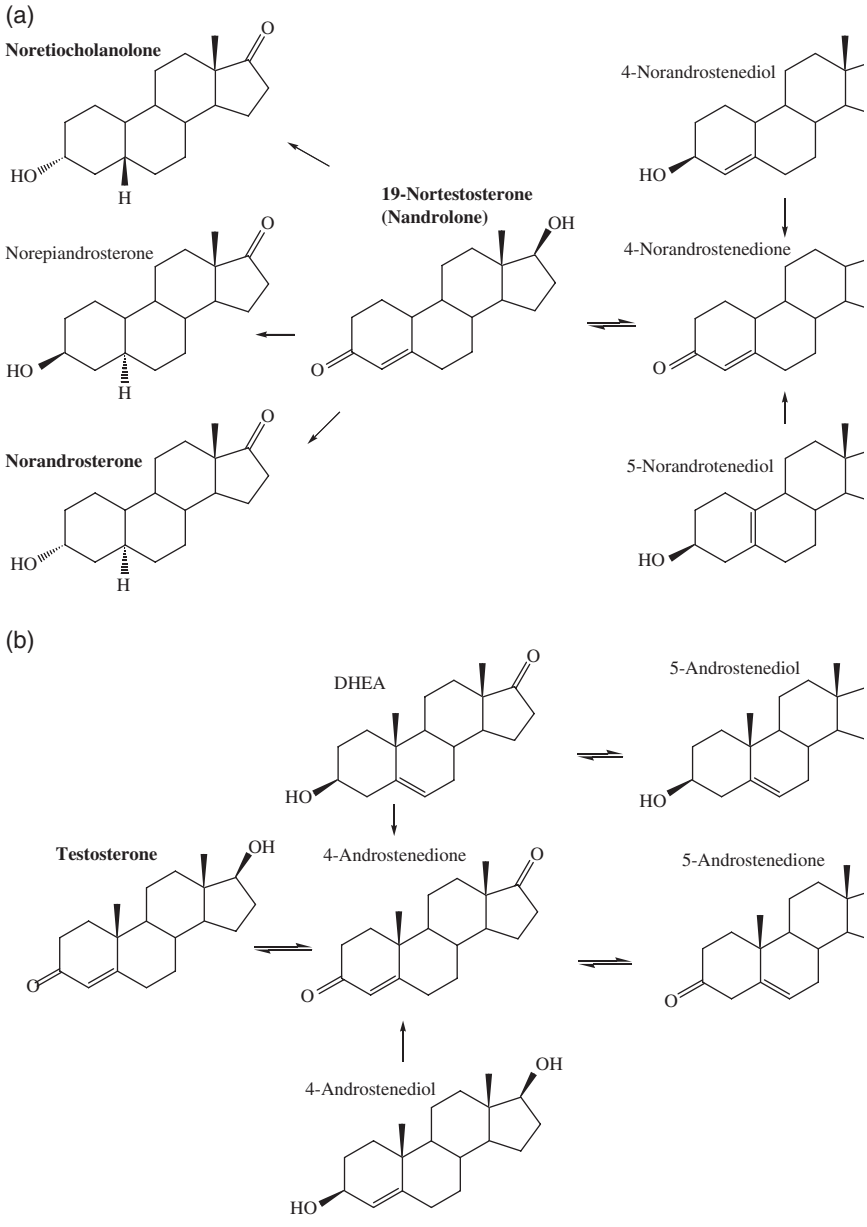

Fig. 1. (a) Precursors (on the right) and main metabolites (on the left) of 19-nortestosterone (nandrolone). (b) Main precursors and the different pathways leading to the testosterone molecule.

quantification was carried out by comparing the normalized areas between the mix standards and the contaminated product.

Excretion studies with contaminated products

The recommended dosage of the contaminated products was prescribed during 1 or more days to volunteers. They collected their urine during 48 h or more after the intake.

The extractions were performed following the procedure for steroid detection used in the laboratory (Barry Sample & Baenziger, 1989; Massé et al., 1989; Donike & Schänzer, 1992)

The MS detector used was a 5973 coupled to a 6890 GC and a 7683 injector acquired from Agilent.

All analyses were performed with an HP 5-MS column (25 m, 0.20 mm, 0.33 μm, J&W Scientific, Folsom, CA, USA). The injection port was maintained at 270 °C and oven conditions started at 100 °C with an initial time of 1 min. The ramp consisted of 16 °C/min to 220 °C and then 3.8 °C/min to 300 °C. The final time was 5 min. All injections were splitless. The MS temperature was maintained at 230 °C.

Results

The purpose of this investigation was to determine the content and the purity of 103 OTC dietary supplements. All the supplements were ordered on different web sites in Europe and in America. The received products were separated into four categories: prohormones, creatine, BCAAs and "mental enhancers" (Table 2).

No stimulant contaminations were found in the analyzed dietary supplements but high amounts of stimulants like caffeine, ephedrine or synephrin were detected in the "mental enhancers" products (data not shown). This are not considered as contaminants as these substances were declared on the labels.

The results of the screening of the 103 products for the presence of steroids parent compounds revealed the presence of metandienone in three different dietary supplements. Similar results have been obtained by two other antidoping laboratories (Gmeiner, 2002; Geyer et al., 2003) (Table 3). Excretion studies were carried out with an oral administration of the recommended dosage of each of these three contaminated supplements. The urine following the intake of 40 mg of the prohormone 34 was collected during 1 week. High urinary concentrations of the metandienone metabolites were detected and traces of these metabolites were found in urine 1 week after the administration (Fig. 3).

No contamination with other steroid parent compound was pointed out by the GC–MS analyses.

Research of the precursors and metabolites of testosterone and nandrolone revealed that 18 products were contaminated. A macro programmation allowed a rapid identification of the substances included in the

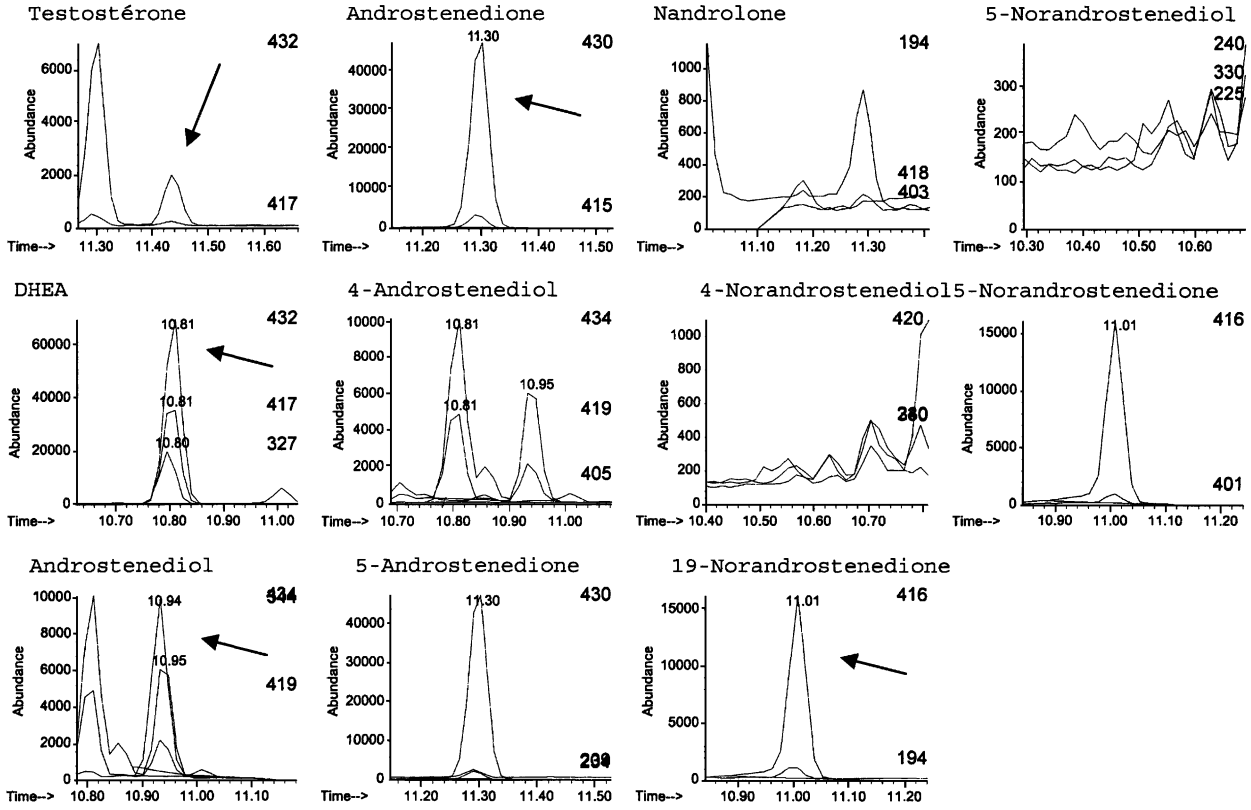

Fig. 2. Macro programmation with chromatograms. Each window contains a research substance with the ions of identification. The arrows point to the peak representing the presence of the mentioned molecule.

Table 2. The four categories in which the 103 complements were dispatched

Class of products	Number of analyzed products	Main claimed compounds	Claimed effects of the products
Prohormone	37	DHEA, androstenediol, androstenedione, norandrostenediol and norandrostenedione	Increase in muscle mass, muscle strength are believed to occur via its conversion to testosterone and other steroids androgenic properties (e.g., as on mood, sexual behavior)
Creatine	42	Creatine monohydrate (pure or conjugated)	Assistance in providing muscle fibers with the energy needed to facilitate quick and forceful movements. More energy storage, increased stamina, strength, protein synthesis and muscle mass
BCAA	12	L-valine, L-leucine, L-isoleucine	Increase glycogen storage and neoglucogenese; increase protein anabolism and decrease catabolism $\Rightarrow$ muscle; accelerate recovery; prevent over-training
"Mental enhancers"	12	Ephedrine, caffeine, Ma Huang, Guarana, Synephrin	Increase blood circulation (brain); help maintain concentration, improve memory and mood; increase metabolic rate and caloric expenditure; fat loss

The number of products, the composition and their main properties are indicated. BCAA, branched chain amino acid.

Table 3. Quantification of the metandienone contaminations

Product	Amount of metandienone (mg/g)		
	Switzerland	Germany	Austria
Prohormone 34	0.67	0.41	0.65
Prohormone 35	0.60	0.96	X
Prohormone 36	15.10	17.30	X

The first product was analyzed in three different laboratories whereas the two others were analyzed only by the Swiss and German laboratories.

supplement composition (Fig. 2). The number of mislabelled supplements represents 18% of the 103 products analyzed. Fourteen of these supplements were in the prohormones, three in the "mental enhancers" and one in the creatine category. The "mental enhancer 8" product was in this category because it was mainly composed of ephedrine, caffeine and synephrin but it also contained androstenediol. The most frequent contaminant was the testosterone parent molecule and the amounts were smaller in the creatine and "mental enhancers" than in the prohormone products (Table 4).

The contaminated supplements, except those of the prohormone category, were orally administered to volunteers. The urine was collected after the intake in order to detect the presence of one or more substances, like nandrolone metabolites, that could generate a positive antidoping test. The most interesting excretion study was carried out with the creatine product. Indeed, the administration of the recommended dosage (5.25 g) led to the presence of noticeable urinary concentrations of 19-norandrosterone and 19-noretiocholanolone (Fig. 4). The concentrations were close to the WADA limit of 2 mg/L defined in the international standards (TD2004MRPL – WADA, 2004).

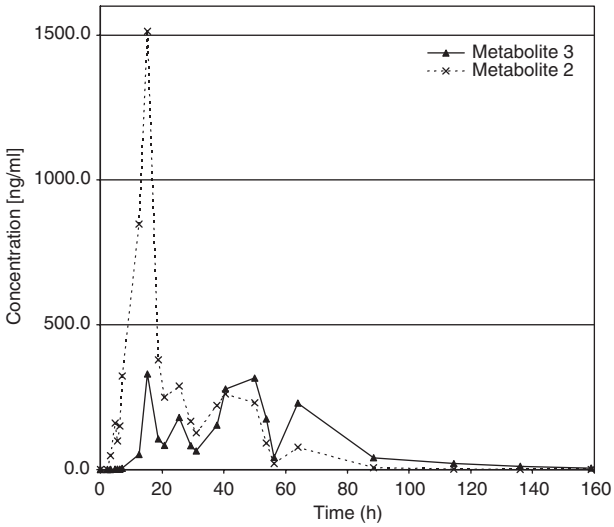

Fig. 3. Urinary excretion of metabolites 2 (m/z 517) and 3 (m/z 358) of metandienone after the intake of the recommended dosage (40 mg/day) of the prohormone 34 contaminated product.

Discussion

Through the daily routine work of an antidoping laboratory, objective information and facts have been pointed out. Indeed, the athletes' declarations in the media or in the antidoping control forms revealed that the dietary supplements are being used more and more by athletes. Considering this information and the fact that their contents are not clearly mentioned, it was in our interest to investigate the OTC supplements. The Council of Europe and the WADA also want governments to work for "safe" supplements. So studies like this one, focusing on the mislabelling of dietary supplements, are needed to evaluate the extent of the problem and to make better recommendations to athletes.

Table 4. Summary of the 18 contaminated products

Product	Weight/cap (g)	Declared compounds	Contaminants	Concentration (. . ./cap)
Creatine 02	0.60	Creatine pyruvate	Adione	390 ng
			DHEA	4900 ng
			Adiol	2500 ng
		Magnesium stearate	NorAdione	1200 ng
			Testosterone	45 ng
"Mental enhancers" 06	0.50	Ephedrine		
		Caffeine	Adiol	600 ng
"Mental enhancers" 07	0.60	Caffeine anhydrous	NorAdione	600 ng
"Mental enhancers" 08	0.55	Adiol	Testosterone	300 μg
Prohormone 01	0.69	Adione, Adiol	Testosterone	2000 μg
Prohormone 02	0.72	19-NorAdione	Adione	2000 μg
Prohormone 05	1.30	19-NorAdione, Adiol, Adione	Testosterone	50 000 μg
Prohormone 06	0.30	Adiol	Testosterone	15 000 μg
			Testosterone	100 μg
Prohormone 07	0.33	19-NorAdiol	DHEA	30 μg
			Nandrolone	1500 μg
Prohormone 11	0.66	Adione	Testosterone	400 μg
Prohormone 13	0.70	19-NorAdiol	Nandrolone	2000 μg
			DHEA	80 μg
Prohormone 15	0.32	Adiol	Testosterone	6500 μg
Prohormone 17	0.59	Adiol, 19-NorAdione	Testosterone	550 μg
Prohormone 18	0.35	Adiol, 19-NorAdione	Testosterone	700 μg
			Testosterone	1100 μg
Prohormone 20	0.36	Adiol	NorAdione	800 μg
Prohormone 21	0.30	Adiol	DHEA	250 μg
Prohormone 27	0.70	Adiol, 19-NorAdione	Testosterone	650 μg
			Adione	200 000 μg
Prohormone 31	0.20	Adiol	Testosterone	500 μg

Adiol, Androstenediol; Adione, Androstenedione; NorAdione, Norandrostenedione.

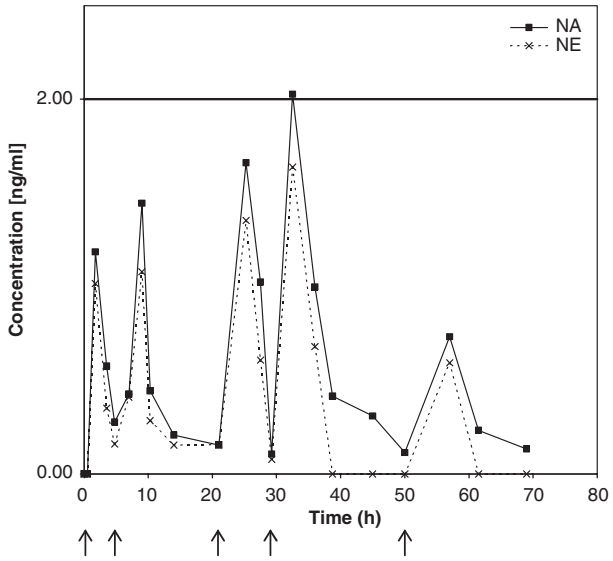

Fig. 4. Urinary excretion of 19-norandrosterone and 19-noretiocholnolone (*m*/*z* 405) after the intake of the recommended dosage (7 caps/day) of the creatine contaminated product. The arrows indicate the intake of the 3 or 4 caps, and the International Olympics committee limit of 2 ng/mL is shown by the bold line.

The steroid parent compounds targeted in this study (Table 1) are the most common steroids found in athletes' urine. Moreover, the prohormones frequently used in the manufacture of such products are androstenedione, androstenediol, DHEA, 19-norandrostenedione and 19-norandrostenediol (Ayotte et al., 2001; De Cock et al., 2001; Green et al., 2001; Pipe & Ayotte, 2002). These molecules are involved in the metabolism of testosterone or nandrolone (Figs 1a and b) and are now on the official list of forbidden substances produced by the WADA (2004). These are the reasons why we focused on the detection of the molecules related to testosterone and nandrolone listed in Table 1. The ions chosen for the identification were normally the most abundant and the most typical for each compound.

The findings of the presence of metandienone in three products were concomitant with the results published previously (Gmeiner, 2002; Geyer et al., 2003). Metandienone is an anabolic steroid that was widely used by athletes in the 1980s. The therapeutical dose for this drug is between 5 and 10 mg/day (Royal Pharmaceutical Society, 1996). Regarding the manufacturer's advice, the intake of the recommended day dosage (40 mg) for the prohormone 34 corresponds to the achievement of about 26 mg of metandienone. The same calculation for the prohormone 36 implies an intake of about 22 mg of metandienone. These high amounts of metandienone could be very harmful for the consumers. Moreover, the numerous adverse effects such as liver dysfunction, increased risk of cardiovascular disease, severe psy-

chological and psychiatric disorders (Royal Pharmaceutical Society, 1996) could be amplified by the supra-therapeutical doses. The analyses of the urines collected following the intake of the supplements revealed the presence of metandienone metabolites (Fig. 3) (Schänzer et al., 1991). Traces of these metabolites were found in urine 1 week after the treatment. These results are very important for the antidoping laboratories and the athletes because by consuming a unique dose of contaminated dietary supplements like the prohormones 34, 35 or 36, the athletes would have trouble with antidoping tests.

The pharmacokinetics (Fig. 3) pointed out a cyclic urinary elimination of the metandienone metabolites. This aspect has never been observed before and further investigations must be conducted to understand this phenomenon.

Considering the contaminations of the supplements with testosterone and/or nandrolone-related substances, the proportion (18%) of mislabelled supplements is in the same range as the previous studies (IOC, 2002). It has to be pointed out that the majority of the contaminations were found in the prohormone category. The presence of substances that are not indicated by the manufacturers is naturally not allowed and a legal procedure may be carried out by the consumers. Nevertheless, people who use prohormones supplements are already exposed, in a conscious or unconscious manner, to the side effects of these substances. Thus, the presence of contaminants like androstenedione or norandrostenediol in the prohormone supplements is not so dangerous as in other supplement types. Indeed, a product such as creatine is usually taken to facilitate quick and forceful movements in providing muscle fibers with the energy needed (creatine-phosphate). Anabolic effects are not the claimed effect of the creatine supplementation. The fact that prohormones are incorporated in the composition of this product could lead to several and unintentional consequences on morphological appearance and behavior. Depending on the time period of the treatment, these psychological and physiological effects could be dangerous and irreversible for the consumer. Nowadays, in terms of doping, the contamination of dietary supplements is a real problem for athletes, sport federations and antidoping laboratories. It appears clearly, in this study, that the intake of the recommended daily dose during 3 days of creatine contaminated with norandrostenedione led to the presence of the two main metabolites of nandrolone in urine with concentrations close to the official limit of 2 ng/mL. With a longer treatment, the concentrations would certainly exceed the limit and the urine sample would be considered as positive for antidoping laboratories. As the creatine product also contained precursors of testosterone, the concentrations of the endogens steroids like androsterone or etiocholanololne were determined (data not shown). No significant change was observed for these steroids and the value of the testosterone/epitestosterone (T/E) ratio, which is commonly used for detection of doping with testosterone (Kicman et al., 1990; Catlin, 1992; Donike et al., 1993), did not vary in a significant manner. These urinary data showed that the hypothalamic–pituitary–gonadal axis is punctually not altered by the intake of contaminated dietary supplements. A prolonged intake of supplement could have more influence on these parameters.

A similar experience was also done with caffeine contaminated with norandrostenedione. Four caps were orally taken (recommended dose) and urine was collected during 3 days. 19-norandrosterone and 19-noretiocholanolone were detected but the concentrations were about 1 ng/mL (data not shown). Probably a longer treatment would have produced higher 19-nortestosterone metabolite urinary concentrations that could imply a positive antidoping test.

Perspectives

This study confirms that supplements contain drugs that will cause the athletes to test positive for substances that are currently on the banned list. The situation in dietary supplements is that there are still approximately one in five supplements on sale that are contaminated – whether accidental or deliberate – with products that are not declared on the label. To date, excretion studies have produced conflicting results with some but not all the subjects who ingested supplements containing prohormones. This shows that the controls made on the purity of dietary supplements are not sufficient. Authorities and sports federations should be aware of this problem and should dictate new regulations for production, sale and use of supplements. These results are also essential to inform athletes and ordinary people of the possible contamination of dietary supplements and to prevent the misuse of such products. Even if the sale of the prohormones has been recently prohibited in the US, these products are still easily available on the internet. This indicates that problems related to the prohormones exist nowadays. Moreover, an important aspect for the consumers is to ask themselves about the use of the dietary supplements as ''ergogenic aids''.

Key words: dietary supplements, prohormones, creatine, urine, doping, anabolic steroids, stimulants.

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