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Review

Comparative analysis of heroin and cocaine seizures

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Abstract

In this brief review the analytical techniques mainly used for comparative analysis of both cocaine and heroin seizures are reported. The characterization of illicit samples is carried out by means of a variety of techniques including thin-layer chromatography, high-performance liquid chromatography, gas chromatography and capillary electrophoresis. By means of these technique it is possible to resolve some component in illicit drugs and their application for comparative analyses is described in this review. Owing to the complexity and the variability of the mixture related to the origin and manufacturing impurities a unique analytical approach based on the application of a single technique it is not sufficient to achieve the requested global characterization of the sample for comparative purposes. Generally a complete characterization is obtained focusing on the identification of minor and major components, origin and manufacturing impurities other than trace compounds such as solvent residues. Nevertheless the application of a single robust methods able to resolve any possible significant marker compounds, is still not described and there is a need for a standardized general procedure suitable for a complete cross-examination of analytical data related to comparative analyses that can be carried out at an international level.

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Contents

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1. Introduction

The international concern about drug abuse requires precise and reliable data on the epidemiology of this phenomenon, which should be apt to be used for both preventive and repressive purposes. Furthermore, the relevance of international traffic of illicit drugs demands updated knowledge of the routes and the distribution network.

To this aim, important information is provided by chemical–toxicological analysis of the samples of confiscated substances. Furthermore, the international character of the cocaine and heroin abuse phenomenon highlights the need that the results obtained can be compared at an international level. For this reason, it is important that illicit drug preparations undergo standardized chemical analyses in order to achieve the best reliability and inter-laboratory comparability.

Nevertheless, it is necessary to keep in mind that the complete characterization of a drug sample coming from an illegal market, done for a comparative purpose, may need various analytical steps and methodological approaches, sometimes very different. In reality these procedures are often difficult to standardize.

However, it is sure that a detailed chemical characterization of a natural or synthetic narcotic is crucial for the success of the many control activities of the illicit drug trading [1–4]. Besides, in illicit drug analysis the identification of minor components, such as, for example, the impurity due to the origin or to the synthesis, is of crucial importance.

During the preparation of an illicit drug, both of natural origin such as cocaine or of a semisynthetic origin such as heroin, all the procedures of extraction, purification, synthesis (or semisynthesis) involve the use of different chemical products (acids, bases, solvents, catalysts, etc.). These may leave traces in the final product or may produce specific alterations in the chemical structure of some of the components of the drug.

The study of these impurities or of the possible degradation products is very useful to trace back to a specific illegal production process and for the comparative analysis of two or more separate drug samples. Furthermore, the so-called origin impurities, i.e., the natural substances that can be found originally in the raw material and that can still be found in traces in the final product in spite of the procedures of extraction, purification and of possible transformation of the initial product, are likewise useful for comparative purposes.

The characterization of all these minor compounds in the drug samples confiscated on different occasions and/or in different places provide unique pieces of evidence in order to prove a common origin. This may allow one to reconstruct the routes of the illegal traffic of the narcotic.

2. Heroin

2.1. Background

All the heroin samples confiscated in the illegal market come directly or indirectly from opium, a substance extracted from the plant *Papaver somniferum*. In fact morphine derives from this plant and heroin is produced from morphine by acetylation of the hydroxyls in the C-3 and C-6 positions.

The *Papaver somniferum* is part of the poppy family (Papaveraceae), herbaceous plants with alternate leaves; the poppy is probably a native plant from the Middle East. It is an annual plant with many known subspecies since the plant is able to hybridize, changing its characters, and these can vary according to the environmental factors. Under these conditions it is difficult to make a classification, but it seems certain that of all the poppy family only *P. somniferum* and *P. setigerum* contain morphine [5]. Opium contains various alkaloids, the most important of which are morphine and papaverine.

The preparation of heroin requires the separation

of morphine from opium [6]. This separation is almost never completely efficient because in the final product not negligible quantities of codeine, papaverine, noscapine and meconine can still be found. Acetic anhydride is used for the acetylation, sometimes together with organic bases, at varying temperatures and times. During the process of acetylation a first intermediate product of the synthesis, 0^3-monoacetyl morphine, is formed. Then heroin is formed, and finally it is in part spontaneously deacetylated into 0^6-monoacetyl morphine.

During this process, if other alkaloids, that can be found as impurities in the original morphine, have functional groups which can react with acetyl radicals, they will produce acetyl derivatives, such as in the case of codeine. If they do not react with acetyl groups, they will remain unchanged in the final product such as for papaverine and noscapine.

If, on the other hand, they are chemically unstable, as in the case of tebaine, they will form a variety of rearrangement and acetylation by-products.

Heroin purification is generally done by separation of the free base in alkaline medium, then crystallization as hydrochloride salt after active charcoal treatment. This general procedure is subjected to many variations including preliminary purification of the morphine, that sometimes is completely omitted effecting a process of acetylation of rough opium, the different procedures of refining heroin and the classic steps of adulteration and dilution carried out during the illegal traffic.

In short the chemical composition of heroin available in the clandestine market depends on many factors, as summarized in Scheme 1. Each one of these theoretically can give way to the presence of specific minor compounds on which the comparative chemical analysis is focused.

On the basis of the presence of specific adulterants and diluents, in addition to some of the principal origin impurities, heroin samples may be roughly divided in three principal types of different geographic origin: heroin from south-west Asia, heroin from south-east Asia and Middle East heroin. These different type of heroin are characterized by different amounts of opium alkaloids and related compounds (i.e., noscapine, papaverine and acetyltebaol) [6–9].

In recent years, initially, the amount of morphine and of acetyl derivatives has been considered with respect to codeine and acetylcodeine, then the quantitative ratios between 0^3-monoacetyl morphine and 0^6-monoacetyl morphine has been considered indicative for the modality of the acetylation process [10,11]. Recently, the identification of tebaine by-products (tebaol, acetyltebaol and phenantrenic derivatives), that result in different amounts during the acetylation process, depending on the temperature and the duration of the process have been pointed out as useful for comparative purposes [12–15].

Besides the presence of meconine [16] and other minor opium alkaloids (such as norlaudanosine) [17] as well as the characterization of the residues of volatile substances [18] or of the trace of metals [19] has been also proposed for a complete chemical analysis of the samples.

Results of in depth chemical analysis performed on various samples of heroin, of known geographic area of production [9,20,21] has been referred, these studies, pointed out the qualitative and quantitative variations that may take place in samples of heroin stored in different ways and for different times, are particularly useful to evaluate the importance of each single compound used in comparative analysis.

Opium composition
Methods used for the extraction of morphine
Morphine acetylation procedures
Purification of the mixture through the addition of different solvents
Base heroin precipitation and its purification
Conversion from base heroin to its hydrochloride salts

Scheme 1. Factors affecting the final composition of illicit heroin.

2.2. Analytic methods

2.2.1. Thin-layer chromatography (TLC) and high-performance thin-layer chromatography (HPTLC)

An initial screening of the heroin samples may be easily done with TLC [22,23], which has the characteristics of being easy, economic and rapid. This analytical method is not only useful to determine the primary alkaloids of opium but also for the identification of other minor compounds deriving from the acetylation process of morphine [13,14].

These techniques were already reported for comparative purposes in 1970 when Curry and Patterson [24] used infrared spectroscopy, TLC and gas–liquid

chromatography to obtain qualitative information concerning the presence of heroin as well as other opium alkaloids in street powder and the determination of adulterating substances.

2.2.2. High-performance liquid chromatography (HPLC)

HPLC [25–29] is applied with great advantages with ultraviolet [8,30] or fluorescence detection [31,32]. In the latter case, the high selectivity of the detector allows one to characterize the illegal samples on the basis of the presence of specific fluorescent substances, linked mainly to the degradation products of tebaine.

Ultraviolet and fluorescence detection can also be used in tandem [12,35]. Also, electrochemical detection has been proposed in order to enhance the sensitivity [33–35,38].

HPLC offers the possibility of direct identification of sugar and other carbohydrates (diluents) [36,37] without derivatization reactions, as is required for gas chromatography (GC). Avoiding any derivatization steps renders the analytical procedure more reproducible when the results are to be compared from data produced by different laboratories.

2.2.3. Gas chromatography and high-resolution gas chromatography (HRGC)

Many of the suggested methods for the chemical characterization of heroin samples are based on the use of gas chromatographic techniques, at the beginning with packed columns [4,10,31,39–41] usually coupled with flame ionization detection (FID) or electron-capture detection (ECD) [10,42,43,49], later with capillary columns [17,21,42,44,57].

With the use of gas chromatographic techniques, problems related to the decomposition and rearrangement phenomena during the analytical process, have been reported [45,46] by different authors. It must be pointed out that the organic compounds found in traces in heroin samples are mainly constituted by degradation products of opium alkaloids produced during the acetylation step [17], so it is crucial to be able to accurately discriminate the compounds really contained in the sample from the possible artefacts produced during the gas chromatographic analysis. In this regard Neumann [46] pointed out that it is not wise to limit the comparative study exclusively to the qualitative profile of the impurities from synthesis process. In fact, it has been shown that even when two samples have the same qualitative profile for minor components, they can derive from different synthesis or semi-synthesis procedures.

These data confirm the necessity of applying different methodological approaches in order to perform an efficient comparative study of separate specimens.

The characterization of the residual solvents as well as any volatile compound used during the illicit manufacturing can be considered a valid aid in comparative analysis. The identification of these solvents has been achieved through head space GC, carried out directly on the clandestine preparations of the drugs [18].

Barnfield et al. [47] suggested, for routine purposes, gas chromatographic analysis without sample pre-treatment for the identification of both the principal components and minor compounds. It was been already stressed [48] the importance in comparative analysis of the quantitative evaluation of morphine and codeine content and their relative ratios. The quantitative evaluation was applied also to the relative content of their products of acetylation (heroin and acetylcodeine). According to these authors, the correlation between the principal opium alkaloids was rather constant in the samples coming from the same illicit batch, and it did not change significantly following adulteration and dilution processes.

Eventually, GC coupled with mass spectrometry (MS) has undoubtedly brought advantages in terms of specificity and sensitivity; GC–MS as been mainly used to identify substances in trace amounts previously not identified by GC–FID. According to the modern literature, GC–MS has to be considered a useful tool for comparative purposes [7,8,50,51].

2.2.4. Capillary electrophoresis (CE)

In the last part of this decade CE has found application for the separation of the acid and neutral impurities in heroin [52,53]. CE has been used with UV or laser-induced fluorescence (LIF) detection, which remarkably increases the sensitivity [52].

This method has shown to be suitable both for heroin samples and for rough opium, however a

careful preparation of the sample before the instrumental analysis is generally required [54].

2.2.5. Gas chromatography combustion isotope ratio mass spectrometry (GCC–IRMS)

Recently, the study of the relative ratios of the natural isotopes of carbon and nitrogen has been proposed as a promising method for the determination of the geographic origin of illicit drugs, and for the comparative analysis. The evaluation of the relative ratio $^{12}C/^{13}C$ may be carried out both directly on the heroin and after hydrolysis.

Thus it is possible to carry out a comparative analysis both on the original product (morphine) and on the end product of the processing (heroin) [55,56].

In fact, the relative amount of the carbon and nitrogen isotopes in a plant and in the product derived from it are characterized by the photosynthesis cycle and by the metabolic cycle of carbon, nitrogen, oxygen and hydrogen uptake [56].

Furthermore, environmental conditions such as humidity, temperature and isotopic composition of environmental carbon dioxide in which the plant has grown may influence the isotopic content.

These concepts applied to comparative analysis of drugs show that this analytical procedure is able to provide data not affected by storage, dilution or adulteration.

2.2.6. Atomic absorption spectroscopy (AAS)

The analysis of traces metals in the comparative field has been proposed rarely, mainly because of problems related to the evaluation of the results. Particularly, it has not been possible so far to find out one or more elements that can be considered as discriminative for comparative tests.

The method is essentially based on the mineralization of the sample by nitric acid followed by AAS [19].

3. Cocaine

3.1. Background

Whole cocaine which is available in the clandestine market comes from the leaves of *Eritroxylon coca*, through a process of extraction with organic solvents followed by various procedures of purification including treatment with potassium permanganate, liquid–liquid extraction and a final conversion from free base cocaine to hydrochloride cocaine [58].

There are four recognized varieties [59–63] of coca plants deriving from two species that contain significant levels of cocaine; they are: *Eritroxylon coca* var. *coca* (ECVC); *E. coca* var. *ipadu* (ECVI); *E. coca* var. *novogranatense* (ECVN); *E. novogranatense* var. *truxillense* (ENVT). Historically, ECVC is the one most used for the preparation of street cocaine.

Due to the coarse clandestine processing, many impurities can be present in the final products introduced into the illegal market.

The origin impurities are minor compounds that can be found in coca leaves (*cis* and *trans* cinnamoylcocaine, tropococaine, hydroxycocaine, trimetoxycocaine, truxillines). Other impurities are related to by-products resulting during the clandestine process.

Among the origin impurities, *cis* and *trans* cinnamoylcocaines are widely studied for comparative purposes, because of their stability and their easy identification, possible with different techniques [64–66].

The truxillines are natural alkaloids that can be found in the coca leaves and their content varies significantly from one sample to another [67]. The variation in truxilline amount depends on the taxonomic variety of the plant used or by different clandestine working procedure.

The identification of these substances in street cocaine samples is quite recent [67,68], even if the presence of α- and β-truxillines in coca leaves has been described by Moore et al. [67] who, for the first time, reported their nine isomers.

The truxillines are quite stable and are not affected by illicit chemical treatment of the drugs. So these compounds are considered suitable tools for comparative analysis; on the other hand their complete identification is not easy and requires sophisticated analytical procedures.

The presence of tropococaine in street cocaine samples seems to be very variable, probably linked to the plant's taxonomy. In fact, its content seems to

be lower in the ECVC type of plant with respect to the ENVN and ENVT types [69–71]. The computerized analysis of relative ratios between tropococaine, norcocaine, cinnamoilcocaines and cocaine has been reported [69].

Benzoylecgonine, ecgonine, ecgonine methylester and benzoic acid, [72–74] are the principal hydrolysis by-products of cocaine. These compounds mainly originate during the purification of the drugs, but they can be also produced by inadequate cocaine storage. Cinnammic acids, truxinic acids and truxillic acids, are other hydrolysis by-products proposed as useful for comparative purposes [75–79].

The N-nor series (*N*-formylnorcocaine, *N*-norcocaine, *N*-benzoylnorecgonine methylester, *N*-norecgonine and *N*-acetylnorcocaine) impurities are due to the use of oxidants during the clandestine production [80–85].

The presence of process by-products can be related also to the pH of the medium during the purification of cocaine. For example Casale [86] points out the phenomenon of epimerization in C-2 position for ecgonine and ecgonine methyl ester when a strong base is employed.

Other rearrangement in cocaine-related alkaloids has been described [82] as results of benzoyl group migration.

So, it is evident that for cocaine comparative analysis many more substances can be considered as marker compounds than those suggested for heroin. Nevertheless a complete cocaine characterization should be carried out by also identifying other minor components such as residual solvents [87,89] and by means of different analytical strategies.

The origin impurities and manufacturing by-products of cocaine are summarized in Scheme 2.

(A) Origin impurities
Cinnamolycocaines, tropococaine, truxilline, hydroxycocaines, trimethoxy analogues of cocaine, cuscohygrine, hygrine

(B) Manufacturing by-products
Oxidation products
N-Norcocaine, *N*-acetylnorcocaine, *N*-formylnorcocaine, *N*-benzylnorecgonine methyl ester, *N*-norecgonine methyl ester

Hydrolyis products
Benzoylecgonine, ecgonine, ecgonine methylester, benzoic acid, cinnammic acids, truxininc and truxillic acids

Solvent residues
Dimethyl ketone, diethyl ether, methyl ethyl ketone, etc.

Scheme 2. Origin impurities and manufacturing by-products of cocaine.

3.2. Analytical methods

3.2.1. Thin-layer chromatography and high-performance thin-layer chromatography

In spite of the increasing availability of high-efficiency chromatographic techniques, TLC continues to be considered by many authors as a useful instrument for analysis and for comparative purposes.

This kind of analytical technique is generally applied to the detection of truxillines for example. For example in a recent work [78], the separation of origin impurities by TLC is described in samples of seized cocaine.

Obviously this technique is often used in parallel with other methods in order to obtain the amount of useful information necessary for a complete characterization of cocaine samples.

Della Casa and Martone [90] described a HPTLC method with direct ultraviolet densitometric measurements of the components found in illicit drug samples. This methods provides also preliminary quantitative information about the relative amount of each component.

3.2.2. Gas chromatography and GC–MS

GC has certainly been one of the most used techniques for the analysis of by-products and impurities of illicit drugs. The chromatographic methods developed for this purpose were first based on packed columns [91,92]; however, due to the complexity of the mixtures associated with the impurities, the packed columns often did not give a sufficient resolution. These problems have been generally overcome by the use of capillary columns. Amongst the detection methods employed, the most commonly used is FID [59,66,68], which has a sufficient sensitivity for the determination of many by-products. For the determination of impurities present at lower concentrations, FID is often replaced by more sensitive detection methods such as nitrogen–phosphorus (NPD) detection [68,69,78] or ECD [77,93,94].

The combination of GC–MS [62,71,95,96] in the last few years also represents a turning-point in this field. The analytical methods usually require a sample pre-treatment, including concentration [69] and/or derivatization [97]. In this approach, as in case of comparative analysis of heroin, problems due to the production of analytical artefacts [72] can sometime arise.

Generally speaking however, the chromatographic techniques in the gas phase seem to offer some advantages with respect to other analytical alternatives, considering also the good standardization of the operative conditions and their diffusion in various laboratories.

Using gas chromatographic techniques very accurate results can be obtained with the identification and quantification of marker impurities useful for comparative purposes [98]. The quantitative analysis of the two cinnamoyl isomers indicating the difference in the different varieties of *Eritroxylon coca* growing in different zones has been reported [91]. GC–MS was used also to highlight a higher concentration in the ENVN type with respect to cocaine of the ECVC type [63].

In addition to the identification of minor alkaloids, the analysis of the residual solvents through headspace (HS) GC is often used for comparative analysis. This kind of investigation is really a complementary technique for the characterization of the impurities due to processing [87–89]. The use of nuclear magnetic resonance (NMR) for the qualitative and quantitative determination of the solvents was also proposed [88]. Morello and Meyers suggested the use of HS-GC and GC–MS with the use of deuterated internal standards [87].

In the field of the analysis of the residual solvents the technique based on solid-phase microextraction (SPME) has been recently described [99].

These studies demonstrate the actual employment in clandestine laboratories of acetates and chlorinated solvents during the production of cocaine other than the use of diethyl ether and acetone, for the preparation of cocaine hydrochloride.

3.2.3. High-performance liquid chromatography

HPLC is another analytical technique frequently used to obtain drug impurity signature profiles. Owing to the presence of many cocaine impurities with low volatility and high molecular mass, HPLC offers some advantage over GC for in-depth analysis of cocaine [75,100].

Le Belle et al. [101] proposed an easy HPLC analytical procedure, suitable for screening purposes, achieving the identification of major components, cocaine impurities as well as adulterants in street samples. The use of an ultraviolet detector operating at two different wavelengths is proposed to better evaluate the relative amount of these compounds respect to the cocaine content, obtaining suitable results also for comparative purposes.

The characterization of the truxillines was carried out with reversed-phase HPLC using a UV detector without any sample pre-treatment [102].

The cinnamoylcocaines, surely the most studied substances in the comparative analysis of cocaine samples, were detected using ion-pair chromatography. By this technique partial resolution with quantitative analysis of the *cis* and *trans* cinnamoylcocaines, cocaine and tropococaine in extract of coca leaves has been reported [64].

The use of HPLC, has been also proposed for the analysis of diastereoisomers (pseudococaine, allococaine and allopseudococaine) of cocaine. This analytical procedures are useful to identify a possible synthetic origin of the cocaine. Natural cocaine is constituted by the *levo* form of cocaine. The other diastereoisomer can be only obtained by chemical synthesis [103–107].

3.2.4. Capillary electrophoresis

Micellar electrokinetic capillary chromatography (MECC) is a promising analytical technique for comparative cocaine analysis [108].

CE was applied to study the relative ratio between cinnamoylcocaine and cocaine [109] and the use of this ratio in comparative analysis of illegal sample has been established. According to this paper the relative amount between cocaine and cinnamoylcocaine could be related also to different geographic origin. Consequently the evaluation of these parameters could give a taxonomic imprinting of great value.

A review of the application of electrokinetic capillary chromatography for the analysis of illicit drugs including heroin and cocaine has been recently published [110]. Due to its efficiency, high selectivi-

ty and general applicability, MECC is widely used for forensic drug analyses however systematic comparative analyses carried out by this analytical methods are still not referred.

3.3. New coca leaves alkaloids

Owing the relevant interest in illicit drug ''signature'' and chemical profiling of minor components of illicit cocaine samples many reports can be recently found in the current literature regarding the identification of new coca leaves alkaloids.

The characterization of these compounds seems to offer a valid chance for comparative purposes.

For example, two hydroxycocaine have been identified in sample of seized cocaine [93], their identification was achieved through mass spectrometric analysis as heptafluorobutyl and trimethylsilyl derivatives. The concentration of these compounds was about 0.01% with respect to cocaine. The presence of these substances is surely an excellent parameter for comparing the samples, but its limitation is mainly due to the relevant complexity of the sample pre-treatment, that appears quite difficult to standardize.

Casale and Moore [71], in a modification of the method proposed by Moore et al. [59], isolated four new compounds and their identification was done through a comparison of their mass spectrum with some standard products synthesized. All four alkaloids have been quantified and resulted to be present in an amount lower than 0.1% with respect to cocaine.

Moore et al. [59] have recently published a review of the literature data regarding in depth chromatographic analysis of illicit cocaine and its precursors. In this review, attention is devoted to the characterization of minor compounds and identification of new alkaloids related to origin impurities (cuscohygrine, hygrine and 3′4′5′-trimethoxy-substituted coca alkaloids).

Finally several new trace level alkaloids from *Eritroxylon coca* or by-products related to chlorinated tropanes were identified in samples of illicit cocaine [111–115].

These traces compound can be successfully used in cocaine signature and comparative analysis.

4. Conclusions

It is common knowledge that chemical characterization of illegal drugs can contribute the success of the control of the illicit drug market.

A variety of sophisticated chemical profiling procedures have been described in the literature for cocaine and heroin analysis. By means of these procedure a wide number of drug-related compounds can be identified in illicit samples and the value of this approach has been recognised by numerous law enforcement institutions.

On this subject, for example, Casale stated ''chromatographic impurities signature profiling analysis procedure determining if two or more exhibits of cocaine came from the same batch would be a tremendous benefit to law enforcement as an investigative tool and can ultimately be used in Judicial proceedings'' [98] and his research group produced a large amount of scientific contribution in the field of cocaine profiling.

Moreover it seems realistic to add that such analytical tool would be successfully used worldwide, with additional benefit to the international law enforcement, only if a standardized and reproducible procedure will be used improving the analytical data exchange between co-operating forensic laboratories. Unfortunately, some unresolved problems still exist.

The main problems related to the selection of a well standardized procedure can be summarized in the following points: (a) identification of well defined number and type of drug congeners useful for comparative purposes; (b) standardization of the procedure suggested for sample preparation, extraction, concentration and derivatization before chromatographic analyses; (c) difficulty to unequivocally chose a unique reliable chromatographic technique and detection system able to resolve greater possible numbers of major and minor components of the illicit drug; (d) global evaluation of results also in terms of ageing of the samples, storage conditions, sunlight exposition, infra-batch variability, analytical artefacts and so on; (e) possibility of data computerization, elaboration and cross-examination between different laboratories.

Even if it is possible to find in the current literature suitable analytical procedures able to ensure good analytical results, only one method gener-

ally is not sufficient for a complete characterization of illicit drug preparations.

In depth analysis requires in fact a variety of analytical techniques in order to reach the goal of full comparative examination of separate specimens of drugs.

Moreover, also when a robust method among those suggested in the literature, can be selected [13,14,63,69,105,116] problems related to the possibility of acquisition of reference material and standard compounds, the evaluation of the accuracy an reproducibility together to the eventual implementation of quality control programs should be considered and resolved in order to completely validate the comparative analytical procedure.

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