Sourcing drugs with stable isotopes

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1 Abstract

Carbon ($\delta^{13}C$) and nitrogen ($\delta^{15}N$) isotope ratios at natural abundance levels are useful tools in determining the region-of-origin for both cocaine and heroin. Here we show that cocaine originating from different geographic regions of South America exhibited pronounced differences in their $\delta^{13}C$ and $\delta^{15}N$ values. The distinct isotope-ratio combinations allow reliable determination of the region-of-origin for the major coca growing regions along the Andean Ridge. We then show that heroin and morphine samples also exhibited significantly different $\delta^{13}C$ and $\delta^{15}N$ values that were correlated with their geographic origin. The distinct isotope ratio combinations allowed for identification of heroin and/or morphine originating from Southwest Asia, Southeast Asia, and South America. Variations in the carbon and nitrogen ratios of intercepted cocaine kilos have been examined. Isotope ratio analyses can be applied to determine both source and trafficking information. These stable isotope ratio measurements are conducted on an isotope ratioing mass spectrometer, routinely require only 1-2 mg per analysis, and can be automated (16-20-minute cycle time).

2 Introduction

Cocaine and heroin are the most widely used narcotic drugs in the Western Hemisphere, and their illicit use spans all economic and social classes. Determination of the geographic origin of illicit cocaine and heroin have been the focal point of intense study by the forensic community for over 2 decades [1, 2]. However, previous studies which have focused upon identification of trace residues present in the illicit drug, or on trace alkaloids coextracted along with the cocaine or morphine, have met with limited success. Although the focal point of previous approaches was to derive a region-of-origin signature, virtually all of the previous studies were instead most useful in determining processing methods used in different regions. While this approach is valuable, it has limited applicability if a drug is transported from one region to the next for final processing before shipment to potential customers. For instance, refined cocaine base is often transported from Bolivia and Peru to Colombia for the final conversion to produce cocaine hydrochloride. For this reason, cocaine samples from Colombia may have originated elsewhere.

It is for this reason that we have used an alternative approach, which involves analyses of the stable isotope composition of an illicit drug. Elements are identified on the basis of the number of protons within their nucleus. While atoms of an element share a common number of protons, they may differ in the number of neutrons contained inside the nucleus. The isotopes of an element denote variations in the number of neutrons. Stable isotopes indicate those isotopes of an element which are stable and that do not decay through radioactive processes over time.

Virtually all elements exist in more than one stable isotopic form, although one isotope is usually much more common than the other [3 - 5]. For instance, hydrogen exists as ^{1}H, which is the most common, and as ^{2}H, which has one additional neutron and is also known as deuterium. Carbon has two common stable isotopes: ^{12}C, which accounts for approximately 99% of all the carbon atoms, and ^{13}C, which has one additional neutron, and is present in only about 1% of all carbon atoms. Isotope ratioing mass spectrometers are used to determine the amounts of different isotopic forms in a compound [6]. This instrumentation can distinguish the very small isotope-composition differences of an element that can exist between compounds originating from different locations. These small isotopic differences among compounds often arise from differences in biological, manufacturing, and physical processes [3 - 5]. For instance, biological and enzymatic processes by plants or microbes might preferentially select against the heavy isotopic form of an element during a synthesis reaction, resulting in a product (such as cocaine) which is depleted in the heavier isotopic form. Physical processes associated with the environment can also result in differences in the abundances of heavy isotopic forms of an element. For instance, consider the oxygen isotopes (^{16}O and ^{18}O) in

precipitation. Rain falling in interior continental regions typically has less ^{18}O than rain falling in coastal regions.

Once a molecule, such as cocaine or morphine, is formed, that molecule will retain its natural stable isotope abundance until the compound is decomposed. Thus, if there were differences in the stable isotope abundances of elements in morphine produced by poppies grown in Southeast Asia versus poppies grown in Southwest Asia, those natural isotopic differences would be maintained. The same would apply for cocaine derived from coca leaves produced in Bolivia versus cocaine derived from coca leaves produced in Colombia. Thus, even though a cocaine sample might be processed from cocaine base to cocaine hydrochloride in Colombia, it would be possible to determine whether that cocaine base seized in Colombia had originated from Colombia or from Bolivia. It is important to emphasize that this approach involves the analyses of stable isotopes at natural abundance levels in illicit drugs. No label is added to the illicit compound, but instead we examine the small naturally occurring differences that are associated with biological and environmental processes in different geographic regions.

Analyses of the small isotopic composition differences among compounds can tell you much about the source materials, geographic origin of that material and/or allow one to distinguish among possible sources of a material. Stable isotope analyses have been utilized for geo-locating a wide variety of biological and non-biological materials, including determination of animal origins such as migrating birds [7], identification of the origins of valuable gems such as emeralds [8], and of the origins of ivory [9]. The application of an isotopic approach to illicit drugs has been hampered more by a lack of sufficient authentic samples of known origin than by the lack of an analytical capacity to detect small isotopic differences or by the lack of theoretical framework for predicting how plants should vary in isotopic composition along geographic gradients.

The basis of isotopic variations in organic matter among plants is becoming increasingly clear. Farquhar and colleagues [10] have developed a theory to explain carbon isotope ratios ($\delta^{13}C$) among plants, and others have shown how fractionation differences result in predictable carbon isotope ratio patterns along ecological gradients [11, 12]. More recently, Martinelli et al. [13] have shown that precipitation and soil type differences among forest types contribute to variations in nitrogen cycling patterns, and therefore also in plant nitrogen isotope ratios ($\delta^{15}N$). Farquhar and colleagues [14] and Roden et al.[15] have developed and tested biochemical models to explain how humidity and water source influence hydrogen (δD) and oxygen ($\delta^{18}O$) isotope ratios of plants.

3 Previous efforts to source cocaine

Refined illicit cocaine is produced from native coca leaf (*Erythroxylum coca* and *E. novogranatense*) in crude jungle laboratories

within Bolivia, Peru, and Colombia. The illicit extraction of cocaine from coca leaves is an unsophisticated process involving multiple extraction and precipitation steps [16]. These crude isolation techniques do not fully isolate the cocaine and numerous other less abundant alkaloids are co-extracted from the coca leaves during the manufacturing process, and are carried through to the final product. About 100 minor alkaloids have been characterized from coca, and differences in trace alkaloids among coca populations appear to be genetically-based [17 - 19]. To date, the most useful discriminatory trace alkaloids for geo-sourcing cocaine are the truxillines and trimethoxycocaine, which can be used to differentiate coca plants of Colombian from Bolivian/Peruvian origin, but otherwise are of limited application in sourcing cocaine.

4 Previous efforts to source heroin and morphine

Heroin is a semi-synthetic product derived from morphine, which in turn is obtained from *Papaver somniferum*. *P. somniferum* is more commonly known as the opium poppy and is the source of the poppy seeds commonly used on bakery items. It is the world's only source for medicinal morphine. Illicit cultivation of the poppy occurs principally in Southwest Asia, Southeast Asia, Mexico, and South America [20]. Morphine is extracted from post-flowering poppy reproductive structures and converted to heroin by reaction with acetic anhydride. The approaches for sourcing heroin have traditionally been to analyze minor constituents, impurities, trace residues, or other components that remain in the heroin mixture after processing has been completed [21- 28]. A number of recent studies have examined the possibility that natural variations in the carbon or nitrogen isotopic composition in morphine, and its derivative heroin, record specific geo-location information [29 - 32]. In each of these works the authors were optimistic about the potential use of isotope ratio analyses for the purposes of sample comparison and/or origin determination.

Since heroin is a derived product, there is the opportunity to both source the origin of morphine, the natural plant product, and acetic anhydride.

5 Approaches for isotopic analyses of acetic anhydride, cocaine, heroin, and morphine

Our hypothesis is that the carbon and nitrogen isotope composition of illicit drugs reflect the result of biochemical and environmental processes. If we examine a cocaine or morphine molecule, the C atoms present in that molecule reflect the result of various plant photosynthetic processes which influenced ^{13}C uptake. Humidity, drought, and photosynthetic pathway are all known to influence the ^{13}C composition of a leaf and its chemical constituents [10 - 12]. In regions with drought and lower humidity, the ^{13}C composition is expected to be greater than in regions with more favorable growth conditions. Thus, in environments which differ in these characteristics, we would

expect the ^{13}C composition of the illicit drug to reflect these climatic differences. A similar argument can be constructed for anticipated variations in the ^{13}C composition of morphine. Equivalent arguments can then be made for differences in the stable isotopic composition of the elements H, N, and O in drug molecules based on known plant physiological and environmental principles [12 - 15].

Analyses of heroin provide an unusual opportunity to not only determine the origin of that illicit drug, but also of the acetic anhydride, which is necessary to convert morphine into heroin. In heroin, 17 of the 21 carbon atoms are derived from the plant product (morphine), while the remaining 4 carbon atoms of heroin are derived from acetic anhydride. It is easily possible to convert a seized heroin sample back into morphine, which then from mass balance considerations allows reconstruction of the ^{13}C composition of the acetic anhydride used to produce the heroin.

6 Analytical approaches

Stable isotope abundances are presented in "delta" notation (δ), with stable isotope abundance expressed relative to a standard, $\delta = (R_{sample}/R_{standard} - 1) \bullet 1000$ ‰, where R is the molar ratio of the heavy to light isotopes (e.g., R = D/H, $^{13}C/^{12}C$, or $^{15}N/^{14}N$). For C and N isotopes, the standards are Pee Dee Belemnite (PDB) for carbon (R = 0.0112372) and atmospheric air (AIR) for nitrogen (R = 0.0036765).

Relatively light elements (such as hydrogen carbon, nitrogen, and oxygen) are typically measured using an gas isotope ratioing mass spectrometer. The mass spectrometer consists of a source to ionize the gas, a flight tube with a magnet to deflect the path of the ionized gas, and a detector system at the end of the flight tube to measure the different isotopic species. First, the element of interest must be converted to a gaseous form for introduction into the mass spectrometer. The most commonly used approaches involve introducing H as H_2, C as CO_2, N as N_2, and O as CO_2. As the gas is introduced into the mass spectrometer, it is ionized by removal of an electron as the gas is bombarded by high energy electrons. Then as the ionized gas travels down the flight tube (under vacuum), the paths of light and heavy isotopic species are deflected differently by the magnet. Detectors are positioned at the end of the flight tube to measure the abundance ratios of the heavy and light isotopic species.

The sample size needed for a routine, high-precision isotope ratio analyses of an illicit drug is 1-2 mg. Typically the drug is placed into a tin and combusted in an elemental analyzer coupled to the mass spectrometer. Oxidizing and reducing columns ensure that all carbon and nitrogen are converted to CO_2 and N_2, respectively. A gas chromatograph is positioned following the elemental analyzer and before the mass spectrometer to separate the CO_2 and N_2 gas as they are carried along by a helium stream. Both the carbon and nitrogen isotope ratios of a sample can be determined on a single

analysis run. Additionally, the C and N peaks are integrated as the gases pass through the GC, so that precise C/N ratios can be determined. The advantage of measuring the C/N ratio is that it is then possible to precisely know the sample purity. A typical sample cycle time for the elemental analyzer, gas chromatograph, and mass spectrometer is 16-20 minutes (sample combustion through complete isotope analyses) and samples are routinely placed on a 20-50 sample wheel which allows for unattended sample analyses. Samples that are 1-2 orders of magnitude smaller can also be analyzed with high precision, but sample handling and analysis time are longer.

7 Carbon and nitrogen isotope variations in cocaine

The vast majority of coca leaf production to produce cocaine in South America occurs in five different regions within Bolivia, Colombia, and Peru. Ehleringer et al. [33] showed that across the entire geographical distribution, the $\delta^{13}C$ and $\delta^{15}N$ of coca leaves varied from -32.4 ‰ to -25.3 ‰ for $\delta^{13}C$ and from 0.1 ‰ to 13.0 ‰ for $\delta^{15}N$. The Putumayo and Caqueta regions of Colombia were distinguishable from each other based on $\delta^{13}C$, as were the Huallaga and Ucayali Valleys from the Apurimac Valley of Peru. Coca leaf from Bolivia was consistently lighter in $\delta^{15}N$ than material from Peru. The heaviest $\delta^{15}N$ occurred in coca leaves from Colombia, while the lightest $\delta^{15}N$ values occurred in coca grown in the Chapare Valley of Bolivia.

Ehleringer et al. [33] used bivariate mean and standard deviation parameters to estimate the frequency of correctly identifying the region-of-origin of these coca leaf samples. They predicted region-of-origin by assigning a sample to that region with which it had the highest probability. Using this approach, Ehleringer et al. [33] accurately predicted the region-of-origin for 90% of the 200 coca leaf samples. Including a quantitative determination of other trace alkaloids in coca leaves, especially truxilline and trimethoxycocaine, contributed additional information, providing a clear separation of the Guaviare and Putumayo-Caqueta regions from locations in Peru and Bolivia. Yet from trace alkaloid analyses, it was not possible to differentiate between Peruvian and Bolivian cocaine. However, these samples were distinguishable based on $\delta^{13}C$ and $\delta^{15}N$ analyses of cocaine and/or coca leaves.

By combining alkaloid and δ analyses, Ehleringer et al. [33] achieved a more powerful means for determining the region-of-origin of cocaine derived from these different regions within South America (Figure 1). Taking advantage of the observation that truxilline content and cocaine $\delta^{15}N$ were positively correlated and that cocaine $\delta^{13}C$ and trimethoxycocaine were negatively correlated, a combination plot revealed that the cocaine samples from different regions cluster into tighter groups based on region-of-origin. Using the same analytical approach as presented above, Ehleringer et al. [33] accurately predicted the region-of-origin for 96% of the 200 cocaine samples.

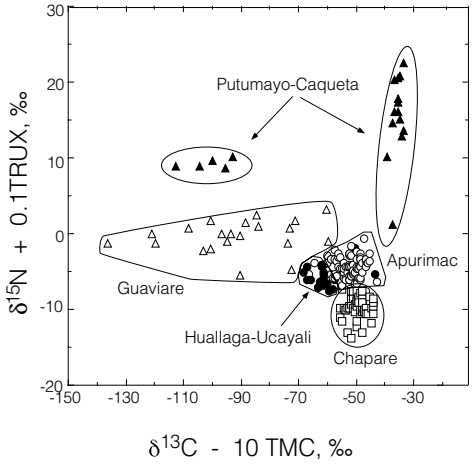

Figure 1. Identification of the regions where cocaine is grown based on a combined model which includes carbon ($\delta^{13}C$) and nitrogen ($\delta^{15}N$) isotope ratios as well as abundances of minor alkaloid components (TMC = trimethoxycocaine, TRUX = truxilline). Symbols are Bolivia (❑), Colombia (Δ), and Peru (❍), with regions within a country distinguished by closed and open symbols. This model correctly identifies the region-of-origin with a precision of 96 %. Data are adapted from Ehleringer et al. [33].

8 Carbon and nitrogen isotope ratio variations in heroin and morphine

Most heroin originates from one of 4 primary regions: Southwest Asia, Southeast Asia, Mexico, and South America. Ehleringer et al. [34] showed that known authentic heroin samples from each of the four growing regions differed by as much as 2.4 ‰ and 3.1 ‰ in their $\delta^{13}C$ and $\delta^{15}N$ values, respectively (Figure 2 left).

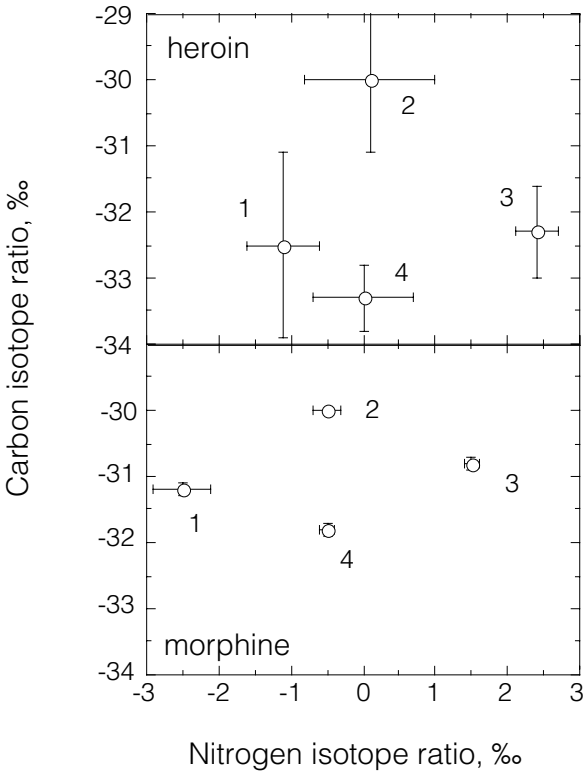

Figure 2. Carbon and nitrogen isotope ratios of bulk heroin samples (top) and the associated extracted morphine (bottom) derived from authentic samples from Mexico (1), Southwest Asia (2), Southeast Asia (3), and South America (4). The data are means and 95% confidence intervals. Data are adapted from Ehleringer et al. [34].

Overall, the $\delta^{13}C$ values for heroin were very light (negative), which is consistent with either plants growing in high humidity environ-ments (usually seen in whole leaf values) and/or compounds resulting from strong secondary isotope fractionation events following photosynthetic carbon fixation. With respect to geo-location

potential, each of the major growing regions were distin-guishable using parametric statistics (Figure 2). The error bars span the 95% confidence interval. There was only limited overlap in the $\delta^{13}C$ and $\delta^{15}N$ values of heroin samples from Mexico and South America. The isotope ratios of samples from Southwest Asia and Southeast Asia samples were statistically distinct from each of the other regions. Considered as single samples instead of as population means, there was limited overlap in the $\delta^{13}C$ versus $\delta^{15}N$ parameter space of individual samples. Two-dimensional $\delta^{13}C$ versus $\delta^{15}N$ realms could be constructed which enclosed the observed variation for heroin and morphine samples from a geographic region.

Specifically for individual heroin samples, only 2 of the 24 South American samples had any overlap with another realm, only 2 of the 20 Southwest Asia samples overlapped with another realm, none of the 26 Southeast Asia samples overlapped with another realm, and none of the 6 Mexico samples overlapped with another realm.

9 Carbon isotope ratio variations in acetic anhydride

Controlling the availability and distribution of acetic anhydride can impact heroin production. Stable isotopes can be used to identify manufacturers of acetic anhydride, particularly within a region. Sampling $\delta^{13}C$ values of acetic anhydride from different manufacturers suggests that there is very limited variation in $\delta^{13}C$ values of individual producers. For example, consider known manufacturers and distributors of acetic anhydride in New Delhi, India (Table 1).

Table 1. Carbon isotope ratio variations (mean and standard deviations) for acetic anhydride derived from different manufacturers and distributors in New Delhi, India. Note that suspected distributors for a known manufacturers are shown immediately following that manufacturer. Distributor 3 is known to import their materials from outside of the region.

	$\delta^{13}C$ (‰)
Manufacturer 1	-11.09 ± 0.04
Distributor 1	-11.11 ± 0.02
Manufacturer 2	-14.00 ± 0.12
Distributor 2	-13.89 ± 0.13
Manufacturer 3	-16.84 ± 0.10
Manufacturer 4	-20.21 ± 0.09
Distributor 3	-29.05 ± 0.02

The variation among samples from a single manufacturer was small enough that it is possible to identify sources that differed in $\delta^{13}C$ by as little as 0.1 ‰. In particular, note that linkages between manufacturer and distributor allows one to precisely confirm these relationships. Seizure evidence also revealed limited $\delta^{13}C$ variation in acetic anhydride containers believed to be of common origin. In analyses of $\delta^{13}C$ values of acetic anhydride from 5 different seizures in 1999 and 2000 (2-10 containers per seizure), the absolute $\delta^{13}C$ variation among containers of common origin was < 0.03 ‰. Typically, the $\delta^{13}C$ standard deviation

among acetic anhydride in containers of common origin was < 0.02 ‰.

We have sampled commercial scientific suppliers of acetic anhydride in different years. Here we note that the manufacturer - isotope patterns remain essentially constant. For instance, in 1999 the $\delta^{13}C$ values of acetic anhydride from Fisher averaged -19.94 ± 0.01 ‰, from Alderich averaged -19.37 ± 0.13 ‰, from Merck averaged -29.16 ± 0.01 ‰, from Matherson averaged -27.18 ± 0.02 ‰, and from Malinkrodt averaged -25.74 ± 0.06 ‰. When comparing these $\delta^{13}C$ values across a 3-year period, the $\delta^{13}C$ values typically varied by less than 0.2 ‰.

10 Purity and isotopic variation within a kilo of cocaine

We have examined the $\delta^{13}C$ and $\delta^{15}N$ variations that occur within and between kilos of cocaine in a common seizure. The purpose of these observations was to examine the extent to which samples were homogeneous and therefore would allow us to use δ values as a tool to reconstruct trafficking and distribution routes. We examined 6 subsamples from 5 different kilos of cocaine seized at the same time. The averages for each of the 5 different kilos reveal limited $\delta^{13}C$ and $\delta^{15}N$ variations in pure cocaine kilos (Table 2). The high cocaine composition is revealed by C/N ratios analyses; a value of 15.4 is expected for pure cocaine. Two of the cocaine kilos exhibited distinct deviations in their C/N ratios. These two samples also exhibited contrasting isotope ratio values. Both the deviations in C/N ratio and in isotope ratio values are consistent with cutting the two cocaine kilos with ~5% caffeine.

Table 2. Carbon isotope ratio (mean and standard deviations), nitrogen isotope ratio (mean and standard deviations), and C/N ratios of bulk cocaine samples from seizures of 5 different kilos.

$\delta^{13}C$ (‰)	$\delta^{15}N$ (‰)	C/N
-35.04 ± 0.04	-5.42 ± 0.16	15.43
-35.06 ± 0.06	-5.76 ± 0.11	15.45
-34.94 ± 0.04	-5.07 ± 0.56	14.04
-34.13 ± 0.14	-7.80 ± 0.39	10.09
-35.22 ± 0.06	-4.03 ± 0.09	15.39

11 Applicability of isotope ratio analyses to trace region-of-origin and to characterize trafficking routes

High precision determination of the region-of-origin of both cocaine and heroin is feasible through automated, routine analyses of $\delta^{13}C$ and $\delta^{15}N$ values [33, 34]. Adding trace alkaloid analyses further increased the precision of the region-of-origin estimate for cocaine [33]. Having an approach which is independent of the mode of converting the original plant product into illicit drug enables a number of strategic options for identifying source regions and trafficking routes. Here we have shown that ecological and isotopic principles [10 - 15] used to predict the $\delta^{13}C$ and $\delta^{15}N$ patterns of plants in different ecosystems can also be applied to determining the distribution of illicit drugs.

With more detailed geographic sampling, we can obtain more precise GIS maps of isotope ratio variations. Such an approach may allow one to identify new regions of the world that might become additional sources of production for these illicit drugs.

On both local and continental scales within the United States, the carbon and nitrogen isotope ratio analyses of illicit drugs should provide federal agencies with an independent quantitative method for determining trade and trafficking distribution routes. The mapping of isotope ratios of seized cocaine and heroin samples within the major cities of the United States will provide a new and valuable tool for directly determining the distribution routes of major cocaine and heroin supplies. Such an approach could also provide a valuable tool for independently assessing the effectiveness of drug eradication programs and for quantifying changes in the sources of illicit drugs as particular drug distributor operations are eliminated.

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12 References

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