



MROALERT

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Updating the Technical,
Legal and Procedural
Aspects of MRO Practice

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MRO Advisory: Possible In Vitro Synthesis of 6-AM from Morphine in GC-MS Analytical Procedures

Caution Advised with the 6-AM Specimen

Heroin is the 3,6-diacetyl ester of morphine (*di (two)-acetyl-morphine*). Heroin is rapidly deacetylated to 6-AM, and 6-AM is deacetylated at a somewhat slower rate to morphine. The presence of 6-AM in a biological specimen rules out poppy seeds. A canon of drug testing and toxicology is that 6-AM (*monoacetyl morphine*) is the no-questions-asked definitive marker for heroin.

There is no acceptable alternative medical explanation for the presence of 6-AM in regulated tests. There has, however, been the occasional anomalous observation of 6-AM over the past decade, and in the past year there has been a cluster of these reports.

Observations and Reports

First Observation: MROs have received laboratory reports of specimens that are 6-AM only. In at least two cases, further testing revealed no codeine and no morphine at all. Further analysis revealed no 6-AM and only morphine.

Second Observation: In a pain management case, a routine UDT was administered, and 6-AM showed up in the urine (morphine was also present). The MRO learned that high levels of morphine had been administered in a hospital for a neck injury. It was highly unlikely that the patient had used heroin during his hospitalization.

Third Observation: Laboratories have reported false-positives for 6-AM on proficiency tests for morphine.

In Vitro Synthesis of 6-AM

In one suspect "6-AM only" case, the laboratory director ran the specimen on an LC-MS (Liquid Chromatography – Mass Spectrometry). As opposed to GC-MS, LC-MS does not require derivatization of the specimen to run on the column.¹ LC-MS allows the specific detection of natural and semi-synthetic opiates and all of their polar metabolites without derivatization and without acidic/enzymatic cleavage of

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conjugates. When LC-MS was utilized, the director found the specimen was negative for 6-AM and positive for morphine.

This is strong evidence of neo-formation, that is, the inadvertent synthesis of 6-AM from morphine in the urine during the derivatization step. Essentially, the laboratory is adding the acetyl group to morphine during derivatization and converting some or all of the morphine in the urine to 6-AM.

In vitro synthesis is also a good explanation for the false-positive observations.

The mere fact that the specimen is positive for 6-AM only does not mean there has been an analytical misadventure. Morphine may be present below the cutoff levels.

MRO Guidance for Management of 6-AM Results

Fortunately, the incidence of 6-AM reports in workplace testing is very low. In a contested case, the MRO should discuss the results with the laboratory director in respect to the integrity of the analytical procedures.

The mere fact that the specimen is positive for 6-AM only does not mean there has been an analytical misadventure. Morphine may be present below the cutoff levels. Some of these cases are resolved by the admission of the donor of heroin use (usually relapse).

In a contested result for a non-regulated test, the MRO could arrange for an LC-MS or HPLC-MS (High Performance) test to be done.

LC-MS is being developed for use in federally regulated testing, but at this time it is not an approved technology. There is, however, more than one way to derivatize morphine, and it is highly unlikely that the inadvertent synthesis would occur when using two different methodologies.

If this is a federally regulated test, the director (RP) will probably have to consult with the regulators to see if this or an alternative approach is allowed.

A Separate Concern: *In Vivo* Synthesis of 6-AM?

It has been shown (unpublished data) that adding aspirin (*acetyl salicylic acid*) to a morphine urine in a simple beaker and heating it up will generate 6-AM. The acetyl group is donated from the aspirin to the morphine.

What has not been shown is whether this transfer of the acetyl group from aspirin to morphine can occur *in vivo*. (This hypothesis is most likely being investigated.)

Guidance on *In Vivo* Formation of 6-AM

The *in vivo* formation of 6-AM is speculative at this time. The concern over publishing the aspirin-to-morphine observation is that MROs will be faced with heroin users with 6-AM urine who claim that they ate a poppy seed bagel and took an aspirin (hence the explanation for both the morphine and the 6-AM found in the specimen). What's next? With two aspirins you get heroin?

This *in vivo* phenomenon may be real, but it has not been observed in a controlled environment, and at the end of the day a new metabolic path should be reproducible.

A good deal of investigation is being done on these issues.

NOTE: The reports to date and observations have all been with urine specimens. There is no reason to believe the same analytical issues would not occur with oral fluid, sweat or hair tests.

MROs are encouraged to report similar anomalous findings to AAMRO. All identifying information in these reports is kept confidential.

1. For more details on laboratory confirmation procedures, see *The Medical Review Officer Handbook, 9th Edition*, Chapter 3.