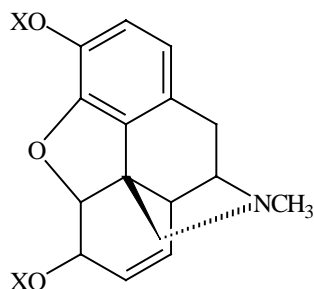


OPIATE CHEMISTRY AND METABOLISM

Opiates are any chemicals derived from morphine and codeine, and morphine and codeine themselves. They all have the generalised structure shown below, where X represents either -H, -CH₃ or -COCH₃.



These chemicals are all pain killers and they all produce drowsiness. Some also produce feelings of euphoria, and they are all to some extent dependence-inducing. For these reasons they are used both medically and illicitly.

To determine whether or not one of these drugs has been taken it is important to understand their respective metabolic pathways (the chain of reactions that they undergo in the body) to know which chemicals are indicative of the use of any opiate and which are indicative of the use of an illicit opiate such as heroin. Once this is known then urine samples can be analysed for these chemicals and a positive identification of the starting drug made.

Of additional interest to the police is the homebake production of morphine. In New Zealand this is commonly done by a method that results in high 3-monoacetyl morphine levels, whereas South-East Asian laboratories commonly produce heroin with high 6-monoacetyl morphine levels. Thus an analysis of the homebake morphine being used gives information as to where the drug originated.

INTRODUCTION

The term “opiates” is used for substances, such as morphine and codeine, which are derived from opium, as well as their chemical derivatives. The best known opiates are heroin, morphine and codeine, the structures of which are given in **Figure 1**. They are all potent narcotic analgesics, i.e. they produce drowsiness and relieve pain.

History

The separation of morphine from opium was first described in 1806. This was a major step forward in understanding the action of natural products that were used at that time in medicine, and stimulated work which led to the isolation of other pure drugs.

From late last century, attempts have been made to chemically alter the structure of morphine to modify its effects and, in particular, to develop a less dependence-inducing drug. Heroin was one of the first such derivatives, prepared by the relatively simple process of acetylation.

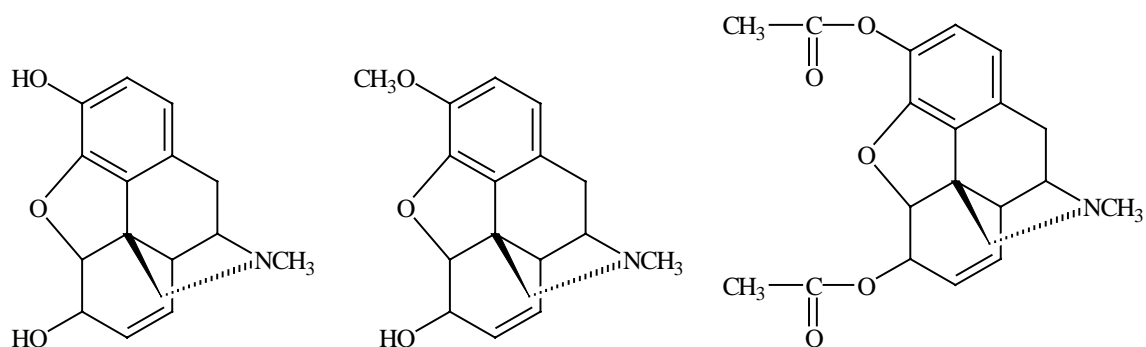


Figure 1 - the structural relationship between heroin, morphine and codeine

A fuller chemical name for heroin is 3,6-diacetylmorphine or diamorphine. **Figure 1** shows the relationship between heroin, morphine and codeine. Initial hopes of reduced dependence liability were soon dashed, but it was found that heroin was a more potent analgesic.

The uses and abuses of opiates

Morphine is an analgesic used for relief of moderate to severe pain, especially that associated with neoplastic disease (tumours), myocardial infarction (heart muscle death) and surgery. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain. Although newer analgesics have been introduced into medicine in recent years and may be superior for particular applications, morphine is still one of the most important drugs in medicine.

Heroin has also been used in medicine. Heroin salts are more soluble than the corresponding morphine salts, allowing smaller volumes to be given by injection, an advantage when used for the relief of severe pain, especially in terminal illness. Use of heroin may be accompanied by a sense of well-being, a reduction in anxiety, and feelings of euphoria. Such feelings enhance the dependence-inducing potential of the drug. While the abuse of opiate drugs is not as large a problem in New Zealand as it is in some countries, the social impact is significant. As well as the physiological effects of opiate dependence, there are hazards associated with a lifestyle involving illegal drug use, including an increased risk of exposure to hepatitis and HIV infection, and the association of drug abuse with crime.

METABOLISM

In the body, all of the opiates are ultimately converted to morphine, and morphine is converted to morphine-3,6-diglucuronide (**Figure 2**). The metabolic pathways of heroin and codeine are briefly described below.

Heroin

Heroin is rapidly metabolised in the body to morphine via 6-monoacetylmorphine. In a death following intravenous injection, neither heroin nor 6-monoacetylmorphine can be detected in post-mortem tissues if the survival time is prolonged. If even traces of 6-monoacetylmorphine are detected in a post-mortem sample of blood, this indicates intravenous use of heroin in the recent past. The presence of 6-monoacetylmorphine also disproves the “poppy seed defence”.

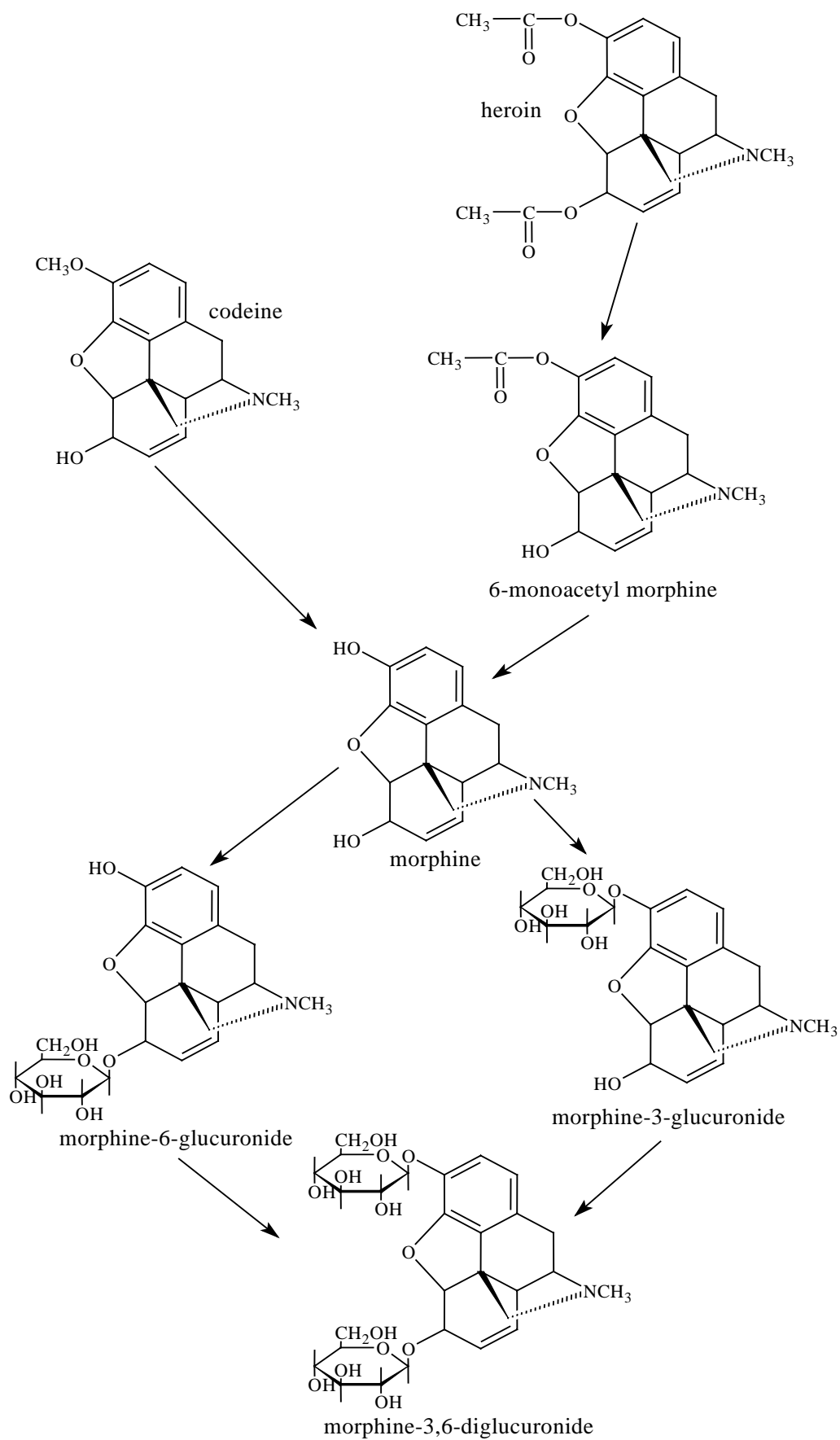


Figure 2 - The metabolic pathway of the opiates

The "poppy seed defence"

Ingestion of products containing opium poppy seeds can result in urine specimens screening positive for opiates because of the presence of traces of morphine or codeine. This has been used as an explanation for a positive urine analysis result. The identification of traces of 6-monoacetylmorphine renders this defence untenable, as this is not part of the metabolic pathway of opium. In toxicology cases, laboratory analysis for opiates therefore includes sensitive checks for the presence of 6-monoacetylmorphine.

Codeine

Codeine is widely used in medicine as an analgesic (although it is less potent than morphine) and as a cough suppressant. In therapeutic doses, codeine is much less liable than morphine to produce adverse effects. The metabolism of codeine includes the formation of a small proportion of morphine. It has been reported that 30 hours after codeine administration, only morphine (which persists longer in the body) may be detectable in the urine by most analytical methods. This has important implications for drug abuse screening programmes when interpreting the significance of low levels of morphine found in a urine sample. Drug abuse screening programmes are widely used overseas, particularly in the USA, in an attempt to identify employees who may represent a safety risk in the workplace. An understanding of the details of opiate metabolism would avoid mistaking a consequence of the medical use of codeine for the more sinister signs of morphine or heroin abuse.

General comments

In post-mortem cases the interpretation of the significance of morphine levels is complicated by the degree of tolerance acquired by addicts who may be able to survive ten times the normal lethal dose. Comparison of drug concentrations in various body samples can help explain the cause of death. For example, if a fatality occurs shortly after ingestion of a drug, the liver levels are likely to be low. On the other hand, relatively high urine to blood or bile to blood concentration ratios in association with low total blood concentrations are indicative of prolonged survival.

The examples given above illustrate why an understanding of opiate chemistry and metabolism is critical to the contribution of illicit drug analysis and toxicology to forensic science.

TESTING FOR OPIATES

Analysis of the samples of opiates for Police and Customs prosecutions under the Misuse of Drugs Act involves the use of some or all of the following techniques: gas chromatography (GC), gas chromatography - mass spectrometry (GC-MS) and high performance liquid chromatography (HPLC). The ratios of various impurities in an opiate sample may be determined to obtain a "profile" of that sample. This can be used to investigate a suspected connection between samples which may have a common origin, and may provide information on the drug distribution network.

As noted above, the presence of 6-monoacetyl morphine is conclusive evidence of the usage of heroin, while the presence of morphine itself can be indicative of the usage of any of the opiates or the eating of poppy seeds. The same applies to the morphine glucuronides.

THE NEW ZEALAND SITUATION

In New Zealand in particular, but also to a limited extent in parts of Australia, shortages of imported heroin have led to the production of “homebake” morphine from pharmaceutical products containing codeine. The “homebake” process involves use of the reagent pyridine hydrochloride to convert the codeine to morphine by removing the methyl- group. The brown morphine powder produced by this process is in the form of crude morphine base. This is generally reacted with acetic anhydride to give a brown or black tarry residue which contains a mixture of heroin, 3- and 6-monoacetylmorphines, morphine and other impurities.

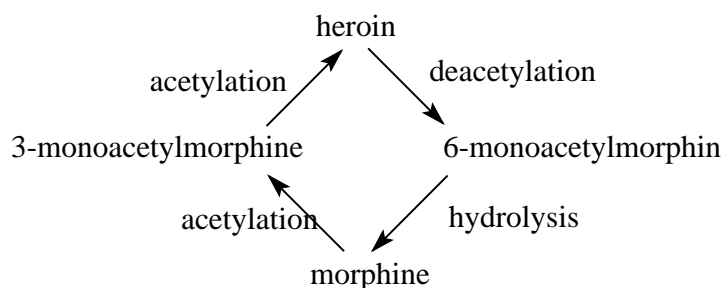


Figure 3 - The relationship between morphine, heroin and the two monoacetyl morphines

New Zealand homebake is unusual in that it contains high levels of 3-monoacetylmorphine, present because of incomplete acetylation of morphine (see **Figure 3**). This is in marked contrast to the usual situation with illicit heroin powder produced, for example, in illicit laboratories in South East Asia, in which the 6-monoacetylmorphine level is higher than that of 3-monoacetylmorphine. Thus the origin of seized drugs can be determined. 3-monoacetylmorphine is relatively unstable with respect to deacetylation, and even heroin itself decomposes (hydrolyses) in the presence of heat and/or moisture.

Written by Dr. Keith Bedford with extensive editing by Heather Wansbrough with reference to: Thompson, Paul Ivan; *Pharmacology of morphine and the active metabolite morphine-6-glucuronide*; University of Auckland; 1991