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SHORT COMMUNICATION

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Analysis of fentanyl and sufentanil in hair by GC/MS/MS

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Abstract Fentanyl and sufentanil are potent narcotic analgesics used only in hospitals as anaesthetic agents. The dependence potential of fentanyl is known. As they are given in doses at the microgram level and their elimination half-life is in the order of a few hours, detection in body fluids is possible only for a short time after administration. Radioimmunological methods are the only ones capable of detecting fentanyl in hair, as normal GC/MS methods for hair analysis are not sensitive enough to detect the drugs after doses in the order of micrograms. We therefore chose GC/MS/MS to analyse fentanyl and sufentanil in two cases where the drugs were given under controlled conditions over several days. The concentration was in the order of less than 100 pg/mg hair.

Key words Fentanyl · Sufentanil · GC/MS/MS · Hair analysis · Drug abuse

Introduction

The first member of the new analgesic class of anilinopiperidines called fentanyl was introduced in 1960 by Janssen (Fentanyl-Janssen). Fentanyl was introduced into the United States in 1968 as a synthetic intravenous anaesthetic/analgesic under the trade name Sublimaze [1]. There are now numerous variations of the parent fentanyl structure in existence, and the derivatives may have a potency exceeding that of fentanyl itself. Some of the derivatives such as sufentanil and alfentanil have great medical importance, and some such as carfentanil are used as immobilizing agents for wild animals. The analgetic potency of carfentanyl is 3200 times higher than morphine [2]. Fentanyl analogues are known in the drug scene to be much more potent than morphine derivatives. There are some illicit analogues, e.g. α-methylfentanyl known as "china white" or "synthetic heroin" and 3-methylfentanyl which is 7000 times as potent as morphine [2]. Documented immunoassay detection of fentanyl in hair was published by Wang et al. [3]. The following report offers the first detection of fentanyl and sufentanil by GC/MS/MS in hair specimens obtained from tumour patients.

Fentanyl, N-(1-phenylethyl-4-piperidyl)-propionanilide (IUPAC) (MW = 336.5) is a synthetic opioid analgesic related to meperidine (pethidine) and with similar properties to morphine [4]. It is used as narcotic agent often in combination with hypnotic drugs, but in a few cases it is also used alone because of the analgesic and sedative effects. In these cases 5–10 μg/kg per hour are administered. It is short-acting after single doses, but it has a relatively long elimination half-life (3-4 h) because of rapid redistribution in the body. About 80% has been reported to be bound to plasma proteins. Fentanyl is usually given intravenously and is used particularly in anaesthesia. The distribution volume is 4 L/kg and pKa 8.4. Fentanyl is capable of producing severe respiratory depression, coma, and hypotension. It is thought to bind to μ-receptors, which are associated with analgesia, respiratory depression, euphoria and physical dependence, occasionally accompanied by spasms of the muscles of the chest wall [5]. The relative analgetic potency of fentanyl is 50-to 100-fold higher than the potency of morphine [6–7]. The minimum lethal dose is reported to be 250 μg [2] and prolonged use of fentanyl may lead to dependence of the morphine type [4].

Sufentanil, N-{4-(methoxymethyl)-1-[2-(2-thienyl)) ethyl]-4-piperidyl}propionanilide (IUPAC) (MW = 386.5) is distributed as Sufenta and the name is derived from

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"Superfentanyl" [8]. Sufentanil has a rapid onset and a shorter duration of action than fentanyl after single doses [4] The pharmacokinetic data are [9]: elimination half time 2–5 h, distribution 1.6–8.7 L/kg, binding to plasma proteins about 93%, pKa 8.01 (citrate). It is also thought to bind to μ-receptors, so the same side-effects as fentanyl are expected. The analgetic potency of sufentanil is sevenfold higher than fentanyl and 1000-fold higher than morphine [10]. The recommended dose in anaesthesia is below 100 μg. Despite high costs sufentanil is administered instead of fentanyl in some clinics. Typical dosages are in the order of 0.2–0.5 μg/kg per hour.

Materials and methods

Hair specimens were taken from a tumour patient who had taken fentanyl for a period of 25 days percutaneously. The daily dose of fentanyl in this medical treatment was 0.6 mg, the total amount being 15 mg.

Hair specimens for sufentanil examinations were taken from a patient who had been intravenously administered the drug over a period of 5 days. The overall intake of this synthetic opioid was 7.75 mg.

The total hair tufts were washed for 1 min in methanol and then acetone. The segment corresponding to the time period of the drug intake was separated and powdered in a ball mill. From each powder 50 mg was incubated in 2 ml Soerensen buffer of pH 7.6 for 2 h at 40° C in a water bath and then centrifuged. The buffer solution was decanted, the residue was shaken again with 2 ml fresh buffer and centrifuged. The combined aqueous layers were extracted with solid phase columns (Chromabond 18 ec) and eluted 3 times with acetone/dichlormethane (3:1). The combined organic phase was evaporated to dryness under a stream of nitrogen. The residue was dissolved in 50 μl methanol and a 3 μl aliquot was injected into the GC/MS/MS system.

Determinations were performed on a Varian 3400 gas chromatograph combining a Finnigan TSQ 700 triple stage quadrupole mass spectrometer as detector (GC/MS/MS). A fused silica capillary column (J&W, DB5, 30m × 0,32mm i.d., 0.25 μm film thickness) was used for GC separation. The GC was programmed in the following way: 2 min at 60° C, 60–300° C at 25° C/min, 3 min at 300° C. The injector (splitless) was controlled with a cold injection system and with solvent purging (Gerstel, Mülheim, Germany), the interface was maintained at 280° C. Helium was used as carrier gas, with a flow rate of 1.0 ml/min. The mass spectrometer was operated in selected reaction monitoring mode. The appropriate molecular ion (MH^+) obtained by chemical impact (CI mode using methane as the reagent gas) was selected as parent mass in the first quadropole. Daughter ions were set in the third quadrupole after collision with argon at a cell pressure of 2.2 mbar, and with a collision energy of –25 eV for the detection of fentanyl or –20 eV for sufentanil.

Results

The determination of fentanyl and sufentanil in the hair extracts are presented in Fig. 1 and 2. Each drug concentration was estimated by comparing the peak area with the area of an external standard of a methanolic drug (dihydrogen citrate) solution.

In the first case a fentanyl concentration of 100 pg/mg hair and in the second case a sufentanil concentration between 5 and 10 pg/mg hair was found.

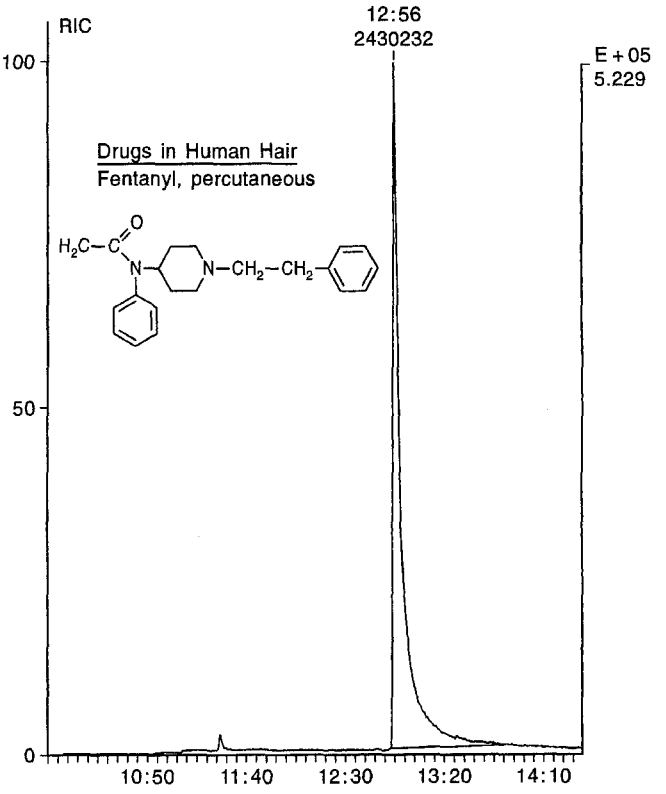

Fig. 1 Reconstructed ion current of a tumour patient's hair extract with residues of fentanyl.

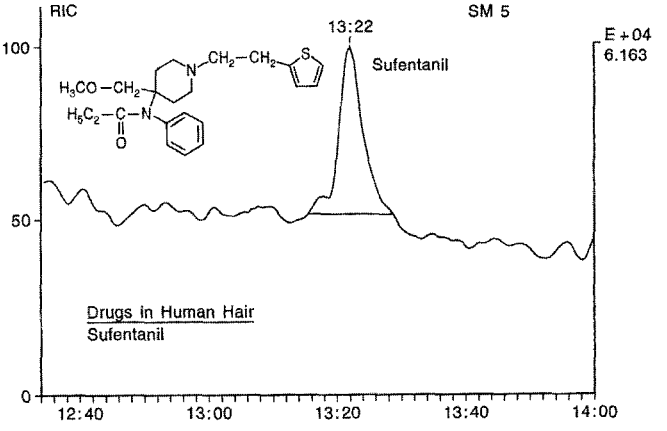

Fig. 2 Reconstructed ion current of a tumour patient's hair extract with residues of sufentanil

Discussion

Fentanyl and sufentanil are potent narcotic analgesics. As the normal therapeutic dose of fentanyl lies below 1 mg, drug abuse is seldom verified. Fortunately, the abuse of fentanyl and its analogues have not been a serious problem in the past. However, these narcotic analgesics are addictive, and have high abuse liabilities [10]. Henderson estimates the number of drug overdose deaths associated with fentanyl-like drugs to be a total of 110 from 1981 to 1987 in California alone [11]. The "rush" is perceived by

addicts as qualitatively similar to that obtained with other narcotics [2]. Also tolerance and physical dependence are similar. As fentanyl and sufentanil are only available in hospitals in most cases physicians and employees are suspected of being opioid addicts, when the drugs are stolen in intensive care units or pain clinics. In forensic toxicology the combination of capillary gas chromatography with tandem mass spectroscopy provides a quick, highly selective and sensitive method for the detection of fentanyl and sufentanil present in methanolic extracts of human hair.

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