REUE | Original Article

Fentanyl and derivatives in patients attended in Emergency Departments: detection with an enzyme immunoassay technique

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BACKGROUND AND OBJECTIVES. Opioids in general and fentanyl in particular are used as recreational drugs. They and their synthetic analogs are considered new psychoactive substances, yet they cannot be detected with the enzyme immunoassays used in Spanish hospitals. This study aimed to detect the use of fentanyl and related synthetics in hospital emergency department patients using a new enzyme immunoassay, and to analyze the test's sensitivity and specificity.

MATERIAL AND METHODS. Prospective observational study to detect and identify fentanyl and its synthetic derivatives in 150 urine samples from patients older than 14 years suspected of drug poisoning or use on admission to 4 hospital emergency departments in the Canary Islands. Patients were screened for fentanyl, acetylfentanyl, and carfentanil with a Randox biochip immunoassay, and the results were confirmed by liquid chromatography with tandem mass spectrometry (LC-MS/MS).

RESULTS. The Randox assay gave positive results for some fentanyl derivative in 27.3% of the samples and specifically for fentanyl in 21 samples (14%). LC-MS/MS confirmed the positive results for fentanyl in 24 samples (16%), but none of the samples positive for acetylfentanyl or carfentanil according to the Randox assay were confirmed by LC-MS/MS. Both the Randox assay and LC-MS/MS found higher percentages of positive results in women ($P < .05$). The sensitivity of the Randox assay was 87.5% for detecting the analyzed derivatives; specificity was 84.1%. Sensitivity for detecting fentanyl itself was 87.5% and specificity was 100%.

CONCLUSIONS. There undetected use of fentanyl by patients attended in emergency departments. The Randox immunoassay facilitates the detection of fentanyl, although more cases should be studied for confirmation, and there is a need for detection of more fentanyl-related opioids in these patients.

Keywords: Fentanyl. Emergency department. Enzyme immunoassay techniques.

Detección de fentanilo y derivados en pacientes atendidos en urgencias hospitalarias, mediante técnica inmunoenzimática

INTRODUCTION. Los opioides y en concreto el fentanilo, se usan como drogas de tipo recreativo y, junto con sus análogos sintéticos, se engloban dentro las drogas conocidas como Nuevas Sustancias Psicoactivas (NPS). Estas sustancias no pueden detectarse con los test de enzimoinmunoensayo usados en los hospitales españoles.

OBJETIVO. El objetivo de este trabajo es detectar el consumo de fentanilo y derivados sintéticos en urgencias, mediante una nueva técnica de detección por enzimoinmunoensayo, así como conocer su sensibilidad y especificidad.

MATERIAL Y MÉTODOS. Estudio observacional prospectivo de detección e identificación de fentanilo y derivados sintéticos en 150 muestras de orina de pacientes mayores de 14 años que ingresaban por sospecha de intoxicación o consumo de drogas en los servicios de urgencias hospitalarios de 4 hospitales de Canarias. Se realizó el *screening* de fentanilo, acetilfentanilo y carfentanilo en las muestras por inmunoensayo Randox® y se confirmaron los resultados mediante cromatografía líquida acoplada a espectrometría de masas (LC-MS/MS).

RESULTADOS. Con el test de Randox, fueron positivas a algún derivado fentanílico el 27,3% de las muestras, y específicamente a fentanilo 21 (14%). Mediante LC-MS/MS se confirmaron 24 muestras a fentanilo (16%). Ninguno de los casos positivos a acetilfentanilo y carfentanilo por Randox, se confirmaron por LC-MS/MS. Hubo un mayor porcentaje de positivos dentro de las mujeres ($p < 0,05$), tanto mediante Randox como por LC-MS/MS. El test Randox presentó una sensibilidad del 87,5% y una especificidad del 84,1%, para la detección conjunta de fentanilo y de derivados analizados, y del 87,5% y del 100% respectivamente para el fentanilo.

CONCLUSIONES. Existe un consumo de fentanilo no conocido hasta ahora en pacientes atendidos en urgencias por consumo de drogas. El método de inmunoensayo Randox® permite la detección de fentanilo, si bien se precisan estudios con mayor número de casos y la inclusión de la detección de un mayor número de opioides derivados del fentanilo.

Palabras clave: Fentanilo. Servicios de Urgencias.Técnica inmunoenzimática.

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Introduction

Opioids are substances widely used in medicine as analgesics. Fentanyl, a synthetic opioid, and its illicitly manufactured analogues are included in the group of drugs known as new psychoactive substances (NPS).[1,2] None of them are detected by the classic immunoassay systems used until now in emergency departments (EDs).[3,4]

In 2021, in the United States, opioids caused 80,411 deaths, of which 87.8% involved synthetic opioids (fentanyl and analogues, and tramadol).[5-8] Their consumption in Spain and other countries is known only through use surveys and by the seizures reported to the Early Warning System of the European Union.[3,9]

Analytical detection tools for NPS using immunoassays on biological samples are now emerging, similar to those used to detect traditional drugs in EDs, although they are still very limited in the number of substances they can detect and their use is not yet widespread in EDs.[10] These tests also serve only for the initial detection of the substance, since confirmatory identification is obtained only when more complex laboratory techniques are used, such as gas or liquid chromatography coupled with mass spectrometry.[3,11-14]

The aim of this study was to detect the possible consumption of fentanyl and its synthetic derivatives in the EDs of the Canary Islands using a qualitative enzyme immunoassay technique on urine samples from patients treated for possible drug consumption, as well as to determine the sensitivity and specificity of this test under real-life conditions.

Material and methods

We conducted a prospective observational study for the detection and identification of fentanyl and its synthetic derivatives in urine samples from patients older than 14 years of age who presented with suspected intoxication or drug consumption at four EDs in the Canary Islands (Spain): *Hospital Universitario de Gran Canaria Dr. Negrín* (Gran Canaria), *Hospital Universitario de Canarias* (Tenerife), *Hospital del Sur de Tenerife,* and *Hospital Universitario Nuestra Señora de la Candelaria* (Tenerife). The study period extended from October 1st, 2019 through May 31st, 2021.

A convenience sample of patients treated for possible NPS drug use was obtained, based on patient or companion history, presence of compatible symptoms, and clinical suspicion by the treating physician, regardless of positive or negative results of conventional urine drug tests. Age, sex, time, day, and month of care were recorded for each patient.

For NPS drug analysis, urine samples were stored at –21°C in each ED until being sent to the Toxicology Service of the *Instituto de Medicina Legal de Las Palmas de Gran Canaria*. In this laboratory, samples were thawed, homogenized, and centrifuged at 10,000 rpm. A total of 200 µL of supernatant were used for analysis with an automated immunoassay biochip (Randox Biochip Assay, Randox Laboratories Ltd, UK). Fentanyl and 2 synthetic derivatives—acetylfentanyl and carfentanil—were detected. The cut-off value was 1 ng/mL for acetylfentanyl and fentanyl, and 1.5 ng/mL for carfentanil.

Confirmation of the biochip results was performed using liquid chromatography coupled to triple-quadrupole mass spectrometry (LC-MS/MS), employing a liquid chromatograph (UHPLC), model 1290 from Agilent Technologies (Santa Clara, CA), equipped with a reverse-phase column. Separation of the different fentanyl compounds from the matrix was achieved using an analytical column (2.1 × 100 mm, 2.7 µm particle size) from Agilent. Two mobile phases were used: mobile phase A consisted of water, 0.1% formic acid, and 2 mM ammonium formate; mobile phase B consisted of methanol, 0.1% formic acid, and 2 mM ammonium formate. The flow rate for both phases was 0.4 mL/min. For confirmation, three certified fentanyl standards previously analyzed with the Randox biochip (acetylfentanyl, carfentanil, and fentanyl) (LGC Standards, Barcelona) were acquired. As the standards were highly concentrated (1,000 ppm in methanol), a 1:100 dilution was performed for each, reaching a final concentration of 10 ppm in methanol to prepare the fortification mixture. To do this, 10 µL of each 1,000-ppm standard were added to a vial, followed by 970 µL of methanol. A calibration curve for urine was constructed using the 3 standards, ranging from 100 to 0.1 ppb. The cut-off value for all three compounds was 0.1 ppb. Water was used as the calibration matrix instead of urine because all urine samples analyzed had been diluted 1:10 with water before injection into the chromatograph, making the matrix effect nearly negligible after dilution and rendering the sample matrix similar to the water used for the calibration curve.

Quantitative variables are expressed as means and standard deviations; qualitative variables as proportions. Proportion comparisons were made with the chi-square test. Independent group comparisons were analyzed with the Mann–Whitney U test. Normality was assessed with the Kolmogorov–Smirnov test. A P-value < .05 was considered significant. Analyses were conducted with SPSS v.21.0.0.

The study was approved by Complejo Hospitalario Universitario de Canarias Ethics Committee (Code: CHUC_2018_84). The principles outlined in the Declaration of Helsinki were followed. Funding was provided by the Fundación Instituto de Investigación Sanitaria de Canarias, 2018 call (reference PIFUN 51/18).

Results

A total of 150 urine samples were analyzed: 96 from men (64%) and 53 from women (36%). One sample lacked recorded sex and was excluded from sex-based proportions. Mean patient age was 36 ± 13.75 years, with no sex-based differences (36 ± 13.01 vs 37 ± 13.08, P = .6).

Table 1 illustrates detection results from the enzyme immunoassay and LC-MS/MS confirmation. Using the Randox test, 41 samples (27.33%) tested positive for some fentanyl derivative: 23 men (23.96%) and 18 women (33.96%) (P = .25). Fentanyl was detected in 21% of samples, with higher detection in women (9.38% vs 22.64%,

Table 1. Analytical results of Randox vs LC-MS/MS and distribution by sex

	Total n (%)	Men n (%)	Women n (%)	*P*
Demographic variables				
Sex	150 (100)	96 (64.43)	53 (35.57)	
Mean age (years)	36.75 (13.75)	36.11 (13.01)	37.9 (13.08)	.6
Positive cases according to analytical method				
Any FD (Randox)	41 (27.33)	23 (23.96)	18 (33.96)	.250
Any FD (LC-MS/MS)	24 (16)	10 (10.42)	14 (26.42)	**.018**
Fentanyl (Randox)	21 (14)	9 (9.38)	12 (22.64)	**.047**
Fentanyl (LC-MS/MS)	24 (16)	10 (10.42)	14 (26.42)	**.018**
Acetylfentanyl (Randox)	21 (14)	10 (10.42)	11 (20.75)	.091
Acetylfentanyl (LC-MS/MS)	0 (0)	0 (0)	0 (0)	NA
Carfentanil (Randox)	25 (16.67)	16 (16.67)	9 (16.98)	.565
Carfentanil (LC-MS/MS)	0 (0)	0 (0)	0 (0)	NA

FD: fentanyl derivative; SD: standard deviation; NA: not applicable; LC-MS/MS: liquid chromatography–tandem mass spectrometry.

Table 2. Sensitivity and specificity of Randox for fentanyl and for any derivative

	LC-MS/MS					
	Fentanyl			Any derivative		
	+	–	Total	+	–	Total
Randox						
+	21	0	21	21	20	41
–	3	126	129	3	106	109
Total	24	126	150	24	126	150
Sensitivity		87,5			8.5	
Specificity		100			84.1	
Positive predictive value		100			51.2	
Negative predictive value		84			97.2	

LC-MS/MS: liquid chromatography coupled to tandem mass spectrometry.

P = .047). Acetylfentanyl was detected in 14% and carfentanil in 16.67%, with no sex-based differences.

Confirmatory LC-MS/MS analysis identified 24 positive samples (16%): 10 men (10.42%) and 14 women (26.42%), *P* = .018. All confirmed cases were fentanyl, and no acetylfentanyl or carfentanil was confirmed.

For detecting any fentanyl derivative using the Randox test, sensitivity was 87.5% and specificity 84.13%, with a negative predictive value of 97.25%. For fentanyl alone, sensitivity was 87.5%, specificity 100%, and positive predictive value 100% (Table 2).

Discussion

To our knowledge, this is the first study in Spain to detect the presence of fentanyl and its derivatives in patients treated in hospital emergency departments for suspected recreational drug use. This figure reached 16% of the samples studied. Considering that only fentanyl and two of its derivatives were assessed, the percentage of positives for fentanyl-related substances could be even higher.

However, our study is based on a convenience sample, not a population-based design, and therefore its data cannot be interpreted epidemiologically as incidence. Another study in Spain, which analyzed the presence of new synthetic opioids in 154 urine samples from patients undergoing treatment for opioid use using chromatographic methods, found fentanyl in 6.1% of samples, while 21.3% reported fentanyl consumption. Furthermore, among the samples positive for fentanyl, half had not consumed it voluntarily.[11]

The opioids with the highest prevalence of use in Spain among people aged 15 to 64 are codeine and tramadol. However, their use has decreased in recent years, while fentanyl and other opioids have increased. In 2022, among people who had ever used opioids, 14% had consumed fentanyl at least once, compared with 1.9% in 2018.[15,16] According to the REDUrHE study, conducted in 11 Spanish EDs across 6 Autonomous Communities between 2017 and 2019, 7.3% of drug-related ED visits were due to opioid use.[17] The indicator "Hospital Emergency Departments related to the non-medical use of psychoactive substances (1978–2020)" shows that in 2020, opioids were involved in 14.3% of drug-related ED visits in Spain. Of these, 6.7% were related to heroin and 8.9% to other opioids (methadone, fentanyl, tramadol, and morphine).[18]

In Spain, according to the EDADES 2022 survey, 15.8% of adults aged 15 to 64 have used opioids at least once, with or without a prescription. Opioid analgesic use is more common among women (16.9%) than men (14.7%). The mean age of onset for prescription or non-prescription opioid use is 34.8 years in men and 35.7 years in women, although non-prescription opioid use occurs at younger ages (26.3 years in men; 24.5 years in women).[15] Our series mirrors these findings: higher positivity among women and similar age patterns.

The higher detection of fentanyl with LC-MS/MS is likely due to the lower cut-off value (0.1 ng/mL) vs Randox (1 ng/mL). Regarding the higher number of positives for fentanyl derivatives with the Randox test, it should be considered that it detects fentanyl with high sensitivity. False positives for acetylfentanyl or carfentanil may arise from several causes. Fentanyl-positive samples may yield false acetylfentanyl positives, as shown in Figure 1, due to cross-reactivity of the Randox technique between acetylfentanyl and fentanyl. Moreover, acetylfentanyl is metabolized predominantly to noracetylfentanyl,[18] a molecule for which we did not have a reference standard to analyze by LC-MS/MS. Nevertheless, small amounts of unmetabolized acetylfentanyl > 0.1 ppb would have been detected by LC-MS/MS, as occurred with fentanyl (< 10% excreted unchanged), since both drugs share highly similar metabolic pathways.[19]

Figure 1 illustrates potential cross-reactivity between carfentanil and remifentanil. Thus, samples containing remifentanil (another synthetic fentanyl analogue) could yield false positives for carfentanil. Therefore, the carfentanil-positive samples detected by Randox but not confirmed via LC-MS/MS may also be due to cross-reactivity with remifentanil, for which no reference standard was available. Another possible explanation for the absence of LC-MS/MS confirmation of carfentanil could be complete biotransformation of carfentanil into metabolites undetect-

Specificity/Cross-reactivity (CR≥20%)

Acetylfentanyl Assay	
Compound (CR%)	
Ocfentanyl (100.0)	Ortho-Fluorofentanyl (59.1)
Furanylfentanyl (65.4)	Cyclopentylfentanyl (129.2)
Acetylfentanyl (84.9)	Para Fluoroisobutrylfentanyl (FIBF) (132.3)
Thiofentanyl (69.0)	Acrylfentanyl (89.8)
Methoxyacetyl Fentanyl (163.9)	Isobutyrylfentanyl (83.5)
Fentanyl (99.3)	Valerylfentanyl (191.1)
Butrylfentanyl (124.8)	(±)-cis-3-methylfentanyl (27.7)
Alpha-Methylfentanyl (31.4)	Cis-Mefentanyl (23.7)
Furanylethylfentanyl (23.6)	Ω-Hydroxyfentanyl (84.7)
Parafluorofentanyl (118.2)	(±)-trans-3-methylfentanyl (32.8)
Tetrahydrofuran Fentanyl (221.8)	Para methoxy-Butyryl fentanyl (HCl) (116.9)
4-Fluoro-isobutyrylfentanyl (80.4)	

Specificity/Cross-reactivity (CR≥20%)

Carfentanil Assay
Compound (CR%)
Carfentanil (100.0)
Remifentanil Acid (60.2)
Alfentanil (48.5)
Norcarfentanil (31.4)

Figure 1. Cross-reactions between fentanyl derivatives in the Randox technique.

able by our LC-MS/MS method. Human in vivo metabolism of carfentanil is largely unknown. However, following the 2002 Moscow Dubrovka Theater incident, in which aerosolized carfentanil and remifentanil were used, urine samples from survivors contained the metabolite methyl-4-((-propionyl) phenylamino) piperidine-4-carboxylate, also known as norcarfentanil[20,21] (Figure 2). We did not have the reference standard to detect this metabolite.

Deville *et al.* evaluated the specificity of the Randox Evidence Investigator® immunoassay for detecting NPS (including fentanyl derivatives) in urine from 41 ED patients. Ten samples tested positive via Randox; only four were confirmed by LC-MS/MS. Among the false positives, four were for carfentanil and two for acetylfentanyl, but none were detected by LC-MS/MS. Reported sensitivity was 100%, and specificity 83.7%, similar to our findings.[10]

Although the source of fentanyl detected in our samples was not investigated—eg, whether medically prescribed or illegally consumed (either voluntarily or involuntarily, as an adulterant)—our findings highlight the need to monitor its possible prevalence among Spanish ED patients. Unintentional fentanyl consumption, through other psychoactive substances adulterated with fentanyl or analogues, may contribute substantially to opioid-related mortality, as users are unaware of its presence. In 2020, there were 974 deaths in Spain due to acute reactions to psychoactive substances, primarily hypnotics (63.3%) and opioids (59.5%). Compared with previous years, opioid-related deaths increased slightly. Opioids were detected in 519 deceased individuals, and in 51.8% of cases, cocaine was also present. Among opioids, methadone was detected in 28.8% of deaths and was the only opioid in 13.3%. There were 20 deaths involving fentanyl and 80 involving tramadol.[18] Recently, the first fentanyl-analogue-related death in Spain was reported.[14]

In the United States, the so-called 4th wave of the opioid crisis—characterized by the combination of stimulants (cocaine, amphetamines) with fentanyl and analogues—has been identified.[22] Nolan *et al.* conducted a study in New York to assess the contribution of fentanyl to cocaine-related overdose deaths between 2015 and 2016. Their findings indicated that fentanyl contamination of cocaine contributed to a sharp increase in cocaine-related overdose deaths. The risk associated with fentanyl-adulterated cocaine is even greater than that associated with fentanyl-adulterated heroin, as cocaine users generally lack the opioid tolerance seen in heroin users.[12]

Limitations

This study has several limitations beyond the convenience sample, which prevents extrapolation of results to estimate fentanyl incidence among intoxicated patients in Spanish EDs. The study was limited to hospitals in the Canary Islands. Additionally, only ED patients—those who experienced significant adverse effects prompting medi-

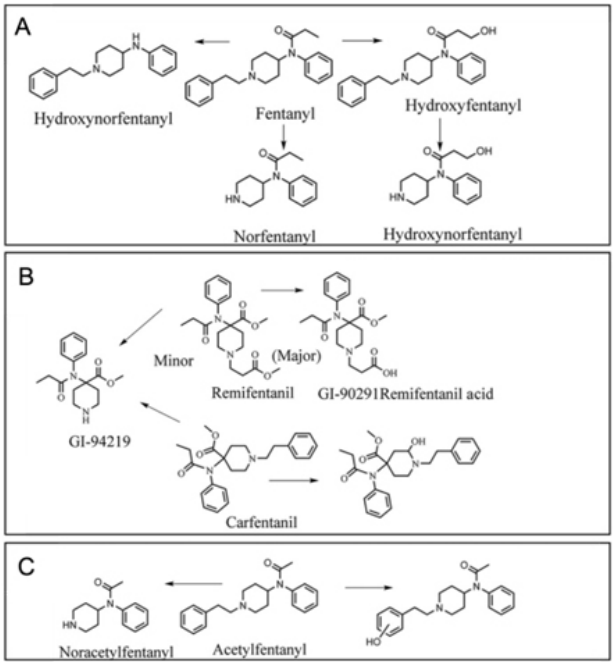

Figure 2. Main metabolites of fentanyl (A), carfentanil (B), and acetylfentanyl (C).

cal attention—were included. Drug detection was not compared with prescribed medications or timing of consumption, which is relevant for interpreting positives in relation to cut-off values.[23] On the other hand, only 2 of the more than 30 known fentanyl derivatives were screened using Randox, excluding users of other derivatives documented by the Early Warning System.[3,16] Reference standards for the metabolites of fentanyl derivatives were not available for LC-MS/MS analysis, limiting detection to parent compounds and excluding derivatives fully metabolized—possibly the case for acetylfentanyl and carfentanil.

Urine positivity indicates fentanyl consumption but does not necessarily mean use occurred on the same day, as 75% of fentanyl is excreted in urine within 72 hours. Doses consumed were unknown, and it is unclear whether ED visits were due to fentanyl or other substances, given the high prevalence of polydrug use in ED patients[24] and in the general population.[15]

Conclusions

The Randox® immunoassay seems to be valid for the detection of fentanyl in urine samples, although a substantial number of false positives for fentanyl derivatives were observed, likely due to cross-reactivity with fentanyl. Studies with larger sample sizes and broader detection of fentanyl derivatives (eg, ocfentanil, cyclopropylfentanyl, remifentanil, or furanylfentanyl) and their metabolites using LC-MS/MS are needed to better characterize real-world sensitivity and specificity and establish the diagnostic utility of this method in EDs, as well as the risk profile of users of these substances. Finally, given the discrepancy between survey data and our findings, incorporating a gender perspective into opioid-use analysis in Spain is essential.

ARTICLE INFORMATION

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