OCFENTANIL

Critical Review Report

Agenda Item 4.5

Expert Committee on Drug Dependence

Thirty-ninth Meeting

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World Health Organization

Contents

Acknowledgements

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Summary

Ocfentanil, a compound structurally similar to the opioid analgesic fentanyl, was developed in the early 1990's with the hope that it would provide a better clinical safety profile than fentanyl. The receptor pharmacology of ocfentanil is not available publicly, but it appears to share pharmacodynamic effects with fentanyl and other μ opioid agonists, including analgesia, sedation, and respiratory depression. In rodents, ocfentanil was approximately 2.5 times more potent as an analgesic than fentanyl and had a shorter duration of action. Because the preclinical research suggested that ocfentanil had a better safety profile than fentanyl, it was selected for clinical evaluation. In humans, however, ocfentanil had a similar potency (3μg/kg ocfentanil produced effects that were comparable to 5μg/kg fentanyl) and side-effects profile as fentanyl so further clinical development was discontinued.

Ocfentanil is not approved in any country for medical use and is under national control in Canada, the United Kingdom, and China.

At least 3 deaths in Belgium and Switzerland related to ocfentanil have been reported. Ocfentanil is currently being sold as heroin but no user discussions of the effects of ocfentanil specifically were found on the Internet. It does not appear to be a common adulterant in heroin, but its high potency is a public health concern in terms of opioid overdose risk.

1. Substance identification

A. International non-proprietary name (INN)

Ocfentanil

B. Chemical Abstract Service (CAS) registry number

101343-69-5

C. Other names

1. UNII-MX52WBC8EV
2. 101343-69-5
3. MX52WBC8EV
4. *N*-(2-Fluorophenyl)-2-methoxy-*N*-(1-(2-phenylethyl)-4-piperidinyl)acetamide
5. Ocfentanilo
6. Ocfentanilum
7. *N*-(2-fluorophenyl)-2-methoxy-*N*-(1-phenethylpiperidin-4-yl)acetamide
8. 1-(2-phyethyl)-4-[*N*-(2-fluorophyenl(methoxyacetamido] piperidinium oxalate
9. Ocfentanil [INN]
10. Ocfentanilum [INN-Latin]
11. Ocfentanilo [INN-Spanish]
12. Ocfentanyl
11. A-3217
12. AC1L1TIK
13. AC1Q4O5M
14. SCHEMBL488987
15. CHEMBL2110917
16. ZINC538120
17. AKOS025401778
18. AC-25508

D. Trade names

None

E. Street names

The street name for ocfentanil might be “synthetic heroin.”

F. Physical properties

Seized samples containing ocfentanil are either a white granular or brown powder


Ocfentanil, paracetamol and caffeine


Ocfentanil, paracetamol, caffeine, and mannitol


Ocfentanil, paracetamol, caffeine, and methamphetamine

(Image taken from: www.wedinos.org/resources/downloads/Philtre_Issue_6.pdf)

G. WHO review history

Ocfentanil has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that ocfentanil is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

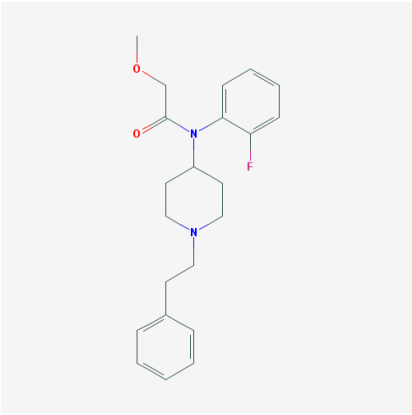
2. Chemistry

A. Chemical name

IUPAC name: *N*-(2-fluorophenyl)-2-methoxy-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide
CA index name: *N*-(2-Fluorophenyl)-2-methoxy-*N*-[1-(2-phenylethyl)-4-piperidinyl]acetamide

B. Chemical structure

Free base:



Molecular Formula: $C_{22}H_{27}FN_2O_2$
Molecular Weight: 370.468 g/mol

C. Stereoisomers

Not applicable.

D. Methods and Ease of Illicit Manufacturing

Ocfentanil synthesis has been described in a patent by Huang et al. 1986

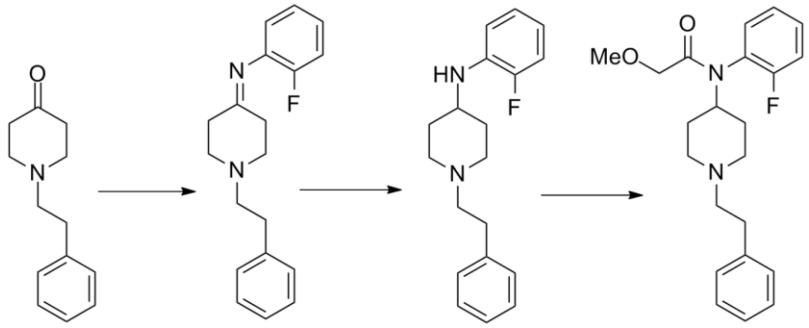


Figure 1: Ocfentanil synthesis (Huang et al., 1986)

Ocfentanil belongs to the 4-anilidopiperidine class of synthetic opioid analgesics that includes fentanyl, sufentanil, alfentanil, and remifentanil. Ocfentanil is comprised of 2 modifications to fentanyl: replacement of the propionamide group with a methoxyacetamide and the addition of ortho-fluorine to the N-phenyl ring.

E. Chemical properties

Ocfentanil "is soluble in aqueous media at a pH below 7 (pKa 7.82) and is stable to moderate heat and light." (Fletcher et al., 1991).
Melting point: 183-184 °C (oxalate) [Huang et al., 1985; patent EP0160422B1 (1985), US4584303A (1986)]

F. Identification and Analysis

Ocfentanil has been analytically confirmed in post mortem samples by ultra-performance liquid chromatography mass spectrometry (UPLC-MS) (Coopman et al. 2016) and in powder samples by gas chromatography coupled to mass spectrometry (GC/MS) confirmed by liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS).

3. Ease of convertibility into controlled substances

No information.

4. General pharmacology

Data on the receptor pharmacology of ocfentanil are not publicly available. As noted by Fletcher et al. (1991), "ocfentanil was developed as one of a series of potent, naloxone-reversible opioids in an attempt to obtain an opioid that had better therapeutic indices in terms of cardiovascular effects and respiratory depression than fentanyl." In preclinical studies, ocfentanil was 2.3 times more potent as an analgesic than fentanyl and its duration

of action was shorter (Bagley et al., 1991). In rodents, ocfentanil appeared to have a larger therapeutic index than fentanyl based on potency ratios between its analgesic effects compared to its effects on respiration and cardiovascular function (Bagley et al., 1991). However, clinical research on its utility as a supplement to general anesthesia described a similar potency between ocfentanil and fentanyl and no clear advantage of the former in terms of safety (Fletcher et al., 1991). In another study in human volunteers, ocfentanil produced a dose-related increase in analgesia and respiratory depression (up to 3 µg/kg; Glass et al., 1989). The pharmacodynamic effects of ocfentanil appear to be similar to fentanyl, a potent agonist at the µ subtype of opioid receptors.

A. Routes of administration and dosage

Ocfentanil can be snorted, smoked, and injected intravenously.

The Welsh Emerging Drugs and Identification of Novel Substances Project reported that samples containing ocfentanil were "snorted/sniff[ed]" or smoked (www.wedinos.org/resources/downloads/Philtre_Issue_6.pdf).

Doses up to 5 µg/kg ocfentanil have been tested intravenously as a supplement to isoflurane anesthesia (Fletcher et al., 1991).

B. Pharmacokinetics

Limited empirical data are available on the pharmacokinetic effects of ocfentanil, but a review of the literature suggests that it has a rapid onset (within minutes) and short duration of action (approximately 1 hour).

In a study in human volunteers, the peak analgesic effects of ocfentanil (up to 3 µg/kg) occurred at 6 min (using tibial and manubrial algesimetry) and had largely dissipated by 1 hr (Glass et al., 1989). Maximal respiratory depression also occurred at 6 min, but was longer lasting than analgesia. Arterial CO_2 tension peaked at 5 min and recovered within 60 and 240 min after administration, with considerable variation in concentration-response after 30 min (Glass et al., 1989).

Drug effects were reported by users of samples that were confirmed by GC/MS and LC/MS/MS to contain ocfentanil (Quintana et al., 2017). One user reported that onset of effects after snorting occurred within about 3 min, with the "real buzz" lasting about 15-20 min and a smaller effect lasting about 1 hour. Another user reported that the effect lasted for 3 hours.

C. Pharmacodynamics

In the mouse hot-plate test, a dose of 0.0077 (0.007-0.013) mg/kg ocfentanil elicited a 50% response (ED_{50}). For comparison, the ED_{50} of fentanyl in the mouse hot-plate test was 0.018 (0.014-0.023) mg/kg. Thus, in mice, ocfentanil was 2.3 times more potent than fentanyl as an analgesic. Its duration of action was 7.8 min and 2.6 min in the rat tail-flick and rat hot-plate tests, respectively. For comparison, the durations of action of fentanyl in these tests were 12.80 and 21.20 min, respectively (Bagley, 1991). Because the therapeutic index was greater for ocfentanil than fentanyl (see below, adapted from Bagley, 1991), it was selected for clinical trials.

Therapeutic Indices for Ocfentanil and Fentanyl in the Conscious, Freely Moving Rat and Isoflurane Anesthetized Rat Models[a] (adapted from Bagley, 1991)

Conscious, Freely Moving Rat			Isoflurane Anesthetized Rat		
	RD[b]		MAPD[c]	HRD[d]	RD
		Tail-Flick Test			
Ocfentanil	7.80		2.20	6.80	5.50
Fentanyl	5.00		0.70	1.90	1.90
		Hot-Plate Test			
Ocfentanil	5.90		1.60	5.20	4.30
Fentanyl	2.50		0.20	0.60	0.60

[a]Therapeutic indices were calculated by dividing the dose that elicited a 50% response (ED_{50}) from control for a specific pharmacological parameter (as determined graphically), by the rat tail-flick or rat hot-plate ED_{50}.
[b]Respiratory depression.
[c]Mean arterial blood pressure depression.
[d]Heart rate depression.

In a study of 32 adult male volunteers, ocfentanil doses (0.03, 0.06, 0.12, 0.24, 0.48, 0.96, 1.92, and 3.84 µg/kg) were administered in ascending order (4 subjects were tested per dose with 3 receiving active ocfentanil and 1 receiving placebo; Glass et al., 1989). Analgesic tolerance was assessed by maximal tolerance to periosteal pressure over the anterior surface of the tibia and manubrium sterni using a spring loaded rod. Ocfentanil produced a dose-related increase in analgesia and $PaCO_2$, but no change in blood pressure or heart rate at any time point or dosage level. In addition, there was no increase in histamine level in response to ocfentanil administration. The analgesic response lasted for approximately 20-40 minutes (Glass et al., 1989).

In a study of 12 patients with significant coronary artery disease, ocfentanil (up to 5 µg/kg) was used in combination with diazepam and scopolamine during elective surgery (Leslie and Hawks, 1990). Compared to placebo, ocfentanil produced greater increases in mean arterial CO_2 without altering heart rate. Loss of consciousness occurred after a dose of 2 µg/kg and all of the patients developed transient apnea; one patient developed possible rigidity.

Ocfentanil was evaluated as a supplement to anesthesia in another study involving 60 patients who were 18-65 years of age and undergoing elective surgery (Fletcher et al., 1991). Intravenous doses of 1, 3, and 5 µg/kg ocfentanil were compared to 5 µg/kg fentanyl. Under these conditions, the 3 µg/kg dose of ocfentanil produced effects (analgesia and sedation) that were comparable to 5 µg/kg fentanyl. The authors concluded that there was no clear advantage of ocfentanil compared to fentanyl.

5. Toxicology

The following are case reports of fatal doses attributed to ocfentanil (adapted from Zawilska, 2017 for first 2 cases):

Gender/age	Case Data	Toxicological Findings	Ref.
M16	A deceased was found dead at home, seated and leaning forward on the toilet. Drug paraphernalia, brown powder in a small zip-locked plastic bag lying on a card with a straw were found at the scene. History of illicit drug abuse and depression.	Ocfentanil: femoral blood, 15.3 ng/mL; heart blood, 23.3 ng/mL; vitreous humor, 12.5 ng/mL; urine 6.0 ng/mL; bile, 13.7 ng/mL; liver, 31.2 ng/g; kidney, 51.2 ng/g; brain, 37.9 ng/g; nose mucus membrane, 2,999 ng/swab. Additionally in peripheral blood: acetaminophen, 45 µg/mL; caffeine, 230 ng/mL.	Coopman, et al., 2016
M24	A deceased was found dead in his apartment. Drug paraphernalia, plastic zipper bag with brown powder, identified as ocfentanil, were found at the scene. At autopsy: lung congestion and edema, brain congestion and edema. History of illicit drug use.	Ocfentanil: peripheral blood, 9.1 ng/mL; heart blood, 27.9 ng/mL; urine, 480 ng/mL. Additionally in peripheral blood: citalopram (130 ng/mL); quetiapine (<10 ng/mL), THC (2.8 ng/mL), and carboxy-THC (<5 ng/mL).	Dussy et al., 2016
M30's	A deceased was found in Belgium in May 2017 following the injection of a powder containing ocfentanil, caffeine, and paracetamol. Other novel psychoactive substances found in his home (etizolam, diclazepam, desoxypipradrol, U-47700, etc.) suggested regular use.	Not reported.	BEWS 2017

Georgetti and colleagues (2017) summarized the case reports by Coopman, et al. (2016) and Dussy, et al. (2016) as follows: "Pulmonary oedema and lung injury" and "Congestion of lungs and brain; slight fatty degeneration of the liver and enlargement of the pituitary gland," respectively.

6. Adverse reactions

Like other µ opioid agonists, ocfentanil has been reported to produce itching, nausea, sedation, and severe respiratory depression. Chest pain, psychosis, and agitation have also been reported, although the authors note that "this information should be taken with caution because other substances may have been involved" (Qunitana et al., 2017)

7. Dependence potential

No empirical data exist on the dependence potential of ocfentanil.

8. Abuse potential

The abuse potential of ocfentanil has not been tested in controlled studies. However, users of samples containing ocfentanil as confirmed by analytical testing (Quintana et al., 2017) reported that "The effect is opiate of course, but not exactly like heroin: more "stimulant," less cool and euphoric. It seems that many people don't see the difference, for example a friend of mine didn't trust me, he was sure it was great heroin. This point is important: only few people have tried real pure heroin so they can easily imagine that there is a difference (I tried medical heroin and I can say it: the effects are exactly the same as street heroin, just less strong!)" Another user reported that "The effect was strong but strange: more stimulant and less euphoric…"

9. Therapeutic applications and epidemiology of medical use

Ocfentanil is not used therapeutically.

10. Listing on the WHO model list of essential medicines

Ocfentanil is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing authorizations (as a medicine)

There are no marketing authorizations as a medicine for ocfentanil.

12. Industrial use

There are no industrial uses for ocfentanil.

13. Non-medical use, abuse, and dependence

Ocfentanil has been reported in Belgium, France and the Netherlands (Coopman, et al., 2016). However, no studies have investigated the prevalence of use of ocfentanil in the general population in these countries.

A recent report noted that "no reports from users claiming to have tested ocfentanil alone or intentionally could be found" and "no advertisements or discussion about trip reports could be found on the web…we hypothesize that its introduction into the market was done by one unique individual or group" (Quintana et al., 2017).

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Public health problems related to misuse, abuse, and dependence

There have been no studies or cases of public health problems such as driving under the influence of drugs (DUID) associated with ocfentanil use.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption, and international trade

None.

16. Illicit manufacture and traffic and related information

Ocfentanil is primarily sold as an adulterant of heroin on the "deep web," defined as "the Internet content [that is] not accessible by traditional search engines, such as Google" (Quintana et al., 2017). Networks, such as Tor, require specific software and configurations in order to be accessed. "Tor allows both user and website anonymization, contributing to the existence of a subset of the deep web known as the hidden web, where illicit drugs can be bought and sold using websites known as cryptomarkets (anonymous markets). The product is paid using anonymous currencies such as BitCoin, and sent to the customer by conventional mail" (Quintana et al., 2017).

Four samples sent to the Asociación Bienestar y Desarrollo, a Spanish non-governmental harm reduction organization that offers anonymous drug checking services, were found to contain ocfentanil (see below table reproduced from Quintana et al., 2017). Gas chromatography coupled to mass spectrometry (GC/MS) confirmed by liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS) were used to analyze the samples. WEDINOS, a British harm reduction organization, "also reported the presence of ocfentanil, paracetamol and caffeine in samples submitted for analysis between March and July 2015 (Wedinos, 2015)."

	Date	Sold as	Appearance	Result	Bought in/sent from	Additional features
Sample #1	June 2015	Heroin	White powder	Ocfentanil, caffeine, paracetamol	Hidden Web, 4/3/2015 Madrid	Vendor: ‘‘FrenchConnection’’ Male, 36 years old
Sample #2	October 2015	Heroin	Not available	Ocfentanil, caffeine (27%), paracetamol (33%), heroin (16%)	Hidden Web, 5/9/2015 France	Vendor: ‘‘Europdrugs’’
Sample #3	October 2015	Heroin	Not available	Ocfentanil, caffeine (26%), paracetamol (29%), heroin (3%)	Hidden Web, 5/9/2015 France	Vendor: ‘‘Europdrugs’’
Sample #4	March 2016	Heroin	White powder	Ocfentanil, caffeine, paracetamol	Hidden Web, 10/3/2016 Madrid	Vendor: unknown Male, 45 years old

FrenchConnection and EuropeDrugs were identified as sources of ocfentanil and both vendors were eventually banned from Alphabay and Nucleus, two of the main deep web marketplaces (Quintana et al., 2017).

17. Current international controls and their impact

Ocfentanil is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and past national controls

Ocfentanil is a controlled Schedule I drug in Canada and a Class A drug in the UK. In China, ocfentanil has been a controlled substance since October, 2015.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other information pertinent to scheduling of the substance

None.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 39th ECDD: Evaluation of Ocfentanil

Please refer to separate Annex 1 document published on ECDD website