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ORIGINAL RESEARCH

Fentanyl Iontophoretic Transdermal System (IONSYS®) can be Safely used in the Hospital Environment with X-Rays, Computerized Tomography and Radiofrequency Identification Devices

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ABSTRACT

Introduction: Fentanyl iontophoretic transdermal system (fentanyl ITS, IONSYS®) is a patient-controlled analgesia system used for the management of acute postoperative pain, designed to be utilized in a hospital setting. The objective of the two studies was to determine if fentanyl ITS could be safely used with X-rays, computerized tomography (CT) scans and radiofrequency identification (RFID) devices.

Methods: The ITS system has two components: controller and drug unit; the studies utilized ITS systems without fentanyl, referred to as the ITS Placebo system. The first study evaluated the effect of X-radiation on the operation of an ITS Placebo system. Five ITS Placebo systems were exposed to X-rays (20 and 200 mSv total radiation dose—the 200 mSv radiation dose represents a tenfold higher exposure than in clinical practice) while operating in the Ready Mode and five were exposed while operating in the Dose Mode. The second study evaluated the effect of RFID (worst-case scenario of direct contact with an RFID transmitter) on the operation of an ITS Placebo system. During these tests, observations of the user interface and measurements of output voltage confirmed proper function throughout all operational modes (Ready Mode, Dose Mode, End-of-Use Mode, and End-of-Life Mode).

Results: The ITS Placebo system met all specifications and no functional anomalies were observed during and following X-ray exposure at two radiation dose levels or exposure at six different combinations of RFID frequencies and field strengths.

Conclusion: The performance of the ITS system was unaffected by X-ray exposure levels well beyond those associated with diagnostic X-rays and CT scans, and by exposure to radiofrequency field strengths typically

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generated by RFID devices. These results provide added confidence to clinicians that the fentanyl ITS system does not need to be removed during diagnostic X-rays and CT scans and can also be utilized in close proximity to RFID devices.

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Keywords: CT scan; Electromagnetic immunity; Fentanyl; IONSYS; Iontophoretic transdermal system; Patient-controlled analgesia; RFID; X-ray

INTRODUCTION

Fentanyl iontophoretic transdermal system (ITS IONSYS®, The Medicines Company, Parsippany, NJ, USA) is a patient-controlled analgesia (PCA) system indicated for the short-term management of acute postoperative pain in adult patients requiring analgesia [1]. It is worn by the patient on the chest or upper outer arm and is self-adhesive. It employs iontophoresis to deliver fentanyl across intact skin which then diffuses into the systemic circulation and is transported to the central nervous system. When the patient activates a dose by double-pressing a button, the system delivers a dose of fentanyl over a period of 10 min [2]. Fentanyl ITS has a well-documented efficacy and safety profile [3–9]. It has been shown to be more efficacious than placebo in three Phase III trials [3–5] and to have similar efficacy to morphine intravenous (IV) PCA in four Phase III trials [6–9]. It was approved for use by the United States (US) Food and Drug Administration (FDA) on April 30, 2015 and by the European Commission on November 19, 2015.

The fentanyl ITS system comprises a controller and a drug unit that are snapped together by the health-care professional before being attached to the patient's chest or upper outer arm [2]. The fentanyl ITS drug unit contains no components or materials that could be affected by diagnostic X-rays, computerized tomography (CT) scans or radiofrequency identification (RFID) transmitters. The fentanyl ITS controller contains semiconductor components that could potentially be affected by radiation from diagnostic X-rays, CT scans or RFID transmitters. The controller has four primary modes of operation as described in Table 1. The fentanyl ITS was tested and verified to be in compliance with International Electrotechnical Commission (IEC) 60601-1-2 (Medical electrical equipment—Part 1–2: General requirements for basic safety and essential performance-collateral standard: electromagnetic disturbances—requirements and tests) at frequencies and field strength levels for a hospital environment. All medical devices must meet this standard to be approved for use. X-rays and CT scans are commonly utilized in the hospital setting as are RFID devices. RFID transmitters are located throughout hospitals including patient rooms and are utilized to track assets (e.g., IV PCA pumps) and monitor patients. The current US prescribing information indicates that fentanyl ITS should be removed prior to X-ray or CT scan and also recommends a separation distance of 2.3 m between fentanyl ITS and RFID transmitters. In these two studies, the function of the fentanyl ITS was evaluated during and after exposure to X-ray and RFID transmitters to determine whether the prescribed separation distance and the removal precautions are necessary.

Table 1 Description of each mode of operation of the fentanyl ITS

Mode	LED	LCD	Audio	Current output
Ready Mode	Slow flashing green	Completed dose count	None	Off
Dose Mode	Fast flashing green	Completed dose count/progress indicator	Single long tone	Enabled
End-of-Use Mode	Off	Flashing completed dose count	None	Off
End-of-Life Mode	Flashing red	Completed dose count	Repeated short tones	Off

ITS iontophoretic transdermal system, *LCD* liquid-crystal display, *LED* light-emitting diode

MATERIALS AND METHODS

The studies utilized an ITS system without fentanyl, referred to as the ITS Placebo system. The ITS controller contains semiconductor components that could potentially be affected by radiation from X-rays, CT scans or from radiofrequency (RF) energy typical of RFID transmitters. The drug unit was not evaluated since it does not contain any components or materials that could be affected by diagnostic X-rays or RF energy from RFID transmitters. The controller unit used in the ITS Placebo systems is identical to the controller unit in fentanyl ITS.

Study 1: Fentanyl ITS and X-Ray Exposure

The objective of the first study was to evaluate the operational performance of the controller unit when exposed to X-radiation exceeding typical ranges for diagnostic X-rays and CT scans. At the start of the study, the controller and the placebo drug unit were assembled. Once assembled, the green light-emitting diode flashed continuously and the liquid–crystal display shows 0 for dose count indicating normal activation of the system. This mode of operation is defined as the "Ready Mode". Five ITS Placebo systems were tested in the Ready Mode and 5 ITS Placebo systems were tested after dose activation (i.e., the dose button had been depressed twice within 3 s to initiate a dose, defined as the "Dose Mode").

The X-ray test equipment was set to 150 kV and to exposure durations necessary to provide radiation doses of 20 and 200 mSv. The 20 mSv dose exceeds the typical range used for both X-ray and CT scan. The 200 mSv dose greatly exceeds the typical radiation dose to simulate multiple exposures or unusual variations in the CT procedure to ensure that the test conditions provided a wide margin of safety.

Each ITS Placebo system in the Ready Mode was connected to a test fixture with a connector for monitoring the electrical performance of the controller. Half of the ITS Placebo systems were activated to enter the Dose Mode. A digital multimeter was connected to the test fixture to record the voltage output from the controller over a 10-min dosing period. System status in the Ready and Dose Modes was monitored throughout the test. The controller output currents were calculated from the voltage measurements using Ohm's law. The nominal target output current of the controller is 170 μA.

Study 2: Fentanyl ITS and RFID Exposure

The objective of the second study was to determine if the controller unit of the fentanyl ITS maintains operational performance when exposed to RFIDs in direct contact with the

controller. While RFID devices are typically positioned at some distance from the patient, direct contact enabled testing of a "worst-case" scenario to fully evaluate safety.

The tests were performed using a set of International Organization for Standardization (ISO) and IEC standards that had previously been developed with AIM Healthcare Initiative and the US FDA [10].

The following frequencies and field strengths representative of RFIDs were tested in direct contact with three ITS Placebo systems: 134.2 kHz at 65 A/m (ISO 14223). 13.56 MHz at 7.5 A/m (IEC 14443 Type A), 13.56 MHz at 7.5 A/m (IEC 14443 Type B), 13.56 MHz at 5 A/m (IEC 15693), 900 MHz at 54 V/m (IEC 18000-6 Type C) and 2.45 GHz at 54 V/m (IEC 18000-4 Mode 1).

The controller and the placebo drug unit were assembled. Each ITS Placebo system in the Ready Mode was then connected to a test fixture with a connector for monitoring electrical performance of the controller. Half of the ITS Placebo systems were activated to enter the Dose Mode. A digital multimeter was connected to the test fixture to record the voltage output from the controller over the 10 min dosing period. System status in the Ready and Dose Modes was monitored throughout the test. The controller output currents were calculated from the voltage measurements using Ohm's law.

System Performance Testing

System performance tests were performed on the ITS Placebo systems after exposure to X-ray and RF radiation. The ITS Placebo systems were checked to determine if they would continue to operate in the Ready and Dose Modes, and automatically transition to the End-of-Use and End-of-Life modes. The controller was designed to operate for 24 h and then enter the End-of-Use Mode; therefore, tests were completed after 24 h, including elapsed time and dose count. The controller was also designed to display the number of doses delivered for 12 h beyond the 24 h use period and then enter the End-of-Life Mode. End-of-Life tests included elapsed time and dose count.

System performance tests included determining: (1) if the system delivered a dose only when the dosing button was pressed twice within 3 s; (2) if the system delivered an output current less than or equal to the maximum specified current of 195.5 μA; (3) if the dosing interval was equal to or less than 11 min; (4) if the system maintained a dose lockout during the dosing period and (5) if the system provided a dose count equal to or less than the number of doses delivered.

Compliance with Ethics Guidelines

This article does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS

Study 1: Iontophoretic Transdermal (ITS) Placebo System and X-Ray Exposure

During and following exposure of the ITS Placebo system to each X-ray energy level, all specifications were met and no anomalies were observed. During X-ray exposure there was no output current detected in Ready Mode, and in Dose Mode the output current was in the range from 169.65 to 171.94 μA (nominal target is 170 μA), which is well within specifications (Table 2). Following X-ray exposure, the ITS Placebo systems remained in Ready Mode and output current was off as expected until the dose

Table 2 ITS placebo system X-radiation test results

System #	System status during the exposure (ready)	Required effective dose (mSv)	Minimum current calculated during the exposure (μA)	Maximum current calculated during the exposure (μA)
1	Ready	20	0	0
		200	0	0
2	Ready	20	0	0
		200	0	0
3	Ready	20	0	0
		200	0	0
4	Ready	20	0	0
		200	0	0
5	Ready	20	0	0
		200	0	0
6	Dose	20	170.08	171.32
		200	169.65	171.19
7	Dose	20	170.57	171.94
		200	170.45	171.69
8	Dose	20	170.08	171.32
		200	169.65	171.19
9	Dose	20	170.2	171.44
		200	170.08	171.32
10	Dose	20	169.65	171.19
		200	169.83	171.07

The exposure time to ensure 200 mSv was 17 min 15 s, the Dose Mode time was about 10 min, and at the end of the Dose Mode the system went back to the Ready Mode for the remaining test time and the voltage recorded was 0 V
ITS iontophoretic transdermal system

button was pressed and released twice within 3 s, when the fentanyl ITS transitioned to Dose Mode, as specified. During Dose Mode after X-ray exposure, additional presses of the dose button had no effect (i.e., the lockout was functioning properly), and output current was in a range from 169.70 to 170.94 μA, which is well within specifications (Table 3). As expected, the ITS Placebo systems automatically transitioned back to Ready Mode after the specified dose duration, and the output current returned to zero. The Placebo ITS systems automatically transitioned as expected to End-of-Use Mode at 24 h (range 23 h, 57 min to 23 h, 59 min) and then automatically transitioned to End-of-Life Mode 12 h later (range 11 h, 57 min to 11 h, 59 min) as expected. As expected, after entering the End-of-Use and End-of-Life Modes, the system appropriately remained off (i.e., no voltage output).

Table 3 ITS Placebo system performance test results after X-radiation exposure

System #	Ready Mode current (μA)	Entered into Dose Mode	Dose Mode current (μA)	Dose duration (min, s)
1	0.000	Pass	169.70	9 min 59 s
2	0.000	Pass	169.95	10 min 0 s
3	0.000	Pass	170.32	10 min 0 s
4	0.000	Pass	170.08	9 min 58 s
5	0.000	Pass	170.94	9 min 59 s
6	0.000	Pass	170.20	9 min 58 s
7	0.000	Pass	170.82	9 min 58 s
8	0.000	Pass	170.20	9 min 59 s
9	0.000	Pass	170.20	9 min 59 s
10	0.000	Pass	169.95	10 min 0 s

ITS iontophoretic transdermal system

Study 2: Fentanyl ITS and RFIDs

During and following exposure to RF radiation at all frequencies tested, the Placebo ITS system met specifications and no anomalies were observed. During RF exposure, there was no output current detected in Ready Mode, and in Dose Mode the output current ranged from 169.74 to 173.66 μA, which is well within specifications (Table 4). The ITS Placebo systems automatically transitioned back to Ready Mode after the specified dose duration, and the output current returned to zero as specified (Table 5). The Placebo ITS systems automatically transitioned to End-of-Use Mode at the specified 24 h with no output voltage. At this point, the system appropriately remained off as expected.

DISCUSSION

Postoperative patients frequently require X-rays or CT scans. CT scans and radiography work on the same basic principle: an X-ray beam is passed through the body where a portion of the X-rays are either absorbed or scattered by the internal structures, and the remaining X-ray pattern is transmitted to a detector (i.e., film or computer screen) for recording or further processing by a computer [11]. Common diagnostic X-ray and CT systems produce (peak) tube potentials in the range of 25–150 kilovolts (kVp). Evaluations of X-ray trends (Nationwide Evaluation of X-Ray Trends) indicate that clinical practice utilizes peak tube potentials up to 109 kVp for X-ray and up to 127 kVp for CT scans [12]. Estimates of the effective dose from diagnostic X-ray are in the range of 0.02–8 millisievert (mSv). Estimates of the effective dose from CT scans are in the range of 2–16 mSv and can vary by a factor of 10 [13]. The results from this study indicate that the fentanyl ITS system will continue to work normally even when exposed to the level of radiation seen in X-rays or CT scans and at a level 25× higher than the typical X-ray and 10× higher than the typical CT scan. In this study, ITS Placebo systems performed as expected in the Ready

Table 4 ITS Placebo system RFID test results

System #	RF exposure condition	Minimum current calculated during the exposure (μA)	Maximum current calculated during the exposure (μA)
11	ISO 14223 134.2 kHz at 65 A/m	169.78	172.43
12	ISO 14223 134.2 kHz at 65 A/m	170.62	173.28
13	ISO 14223 134.2 kHz at 65 A/m	169.74	172.42
14	IEC 14443 Type A (13.56 MHz) 7.5 A/m	170.38	172.29
15	IEC 14443 Type A (13.56 MHz) 7.5 A/m	170.91	173.66
16	IEC 14443 Type A (13.56 MHz) 7.5 A/m	170.37	172.99
17	IEC 14443 Type B (13.56 MHz) 7.5 A/m	169.87	172.55
18	IEC 14443 Type B (13.56 MHz) 7.5 A/m	170.01	172.72
19	IEC 14443 Type B (13.56 MHz) 7.5 A/m	170.45	173.21
20	IEC 15693 (13.56 MHz) 5 A/m	170.32	172.94
21	IEC 15693 (13.56 MHz) 5 A/m	170.29	172.99
22	IEC 15693 (13.56 MHz) 5 A/m	170.05	170.19
23	IEC 18000-6 Type C (900 MHz) 54 V/m	170.00	170.14
24	IEC 18000-6 Type C (900 MHz) 54 V/m	169.96	170.08
25	IEC 18000-6 Type C (900 MHz) 54 V/m	170.10	170.22
26	IEC 18000-4 Mode 1 (2.45 GHz) 54 V/m	170.42	172.92
27	IEC 18000-4 Mode 1 (2.45 GHz) 54 V/m	170.60	173.25
28	IEC 18000-4 Mode 1 (2.45 GHz) 54 V/m	170.10	172.26

ITS iontophoretic transdermal system, *RFID* radiofrequency identification, *RF* radiofrequency

Mode with the dose current off and in the Dose Mode when the nominal target dose current of 170 μA was administered for 10 min. It is important to note the ITS continued to operate as expected even though radiation exposure was 10× the normal level. These data support the conclusion that the fentanyl ITS can be used safely and effectively when exposed to diagnostic X-rays or CT scans, and therefore the system does not need to be removed from patients.

However, as with other radio-opaque devices, health-care providers do need to consider placement of the fentanyl ITS and potential X-rays and CT scans, because while radiation does not affect the system, it is radiopaque and therefore could obstruct the X-ray or CT scan image. For example, if a patient needs a chest X-ray postoperatively, it would be advisable to place the system on the arm; conversely, if the patient has some reason to need an upper arm or shoulder X-ray, then the system can be placed on the chest or the opposite arm. The small system size and the site placement options for the system are versatile enough that with some forethought it should not create an issue with radiology.

Table 5 ITS Placebo system performance test results after RFID exposure

System #	Ready Mode current (μA)	Entered into Dose Mode	Dose Mode current (μA)	Dose duration (min, s)
11	0	Pass	169.96	9 min 58 s
12	0	Pass	170.65	9 min 59 s
13	0	Pass	169.79	9 min 58 s
14	0	Pass	170.29	9 min 59 s
15	0	Pass	170.90	10 min 01 s
16	0	Pass	170.54	10 min 01 s
17	0	Pass	169.87	10 min 01 s
18	0	Pass	170.00	9 min 57 s
19	0	Pass	170.49	9 min 59 s
20	0	Pass	170.40	9 min 58 s
21	0	Pass	170.28	9 min 59 s
22	0	Pass	170.16	9 min 59 s
23	0	Pass	170.08	9 min 58 s
24	0	Pass	169.95	9 min 58 s
25	0	Pass	170.20	9 min 59 s
26	0	Pass	170.60	9 min 59 s
27	0	Pass	170.40	10 min 00 s
28	0	Pass	170.16	10 min 00 s

ITS iontophoretic transdermal system, *RFID* radiofrequency identification

It is important to note that fentanyl ITS is not compatible with magnetic resonance imaging (MRI). Fentanyl ITS contains metal parts and therefore must be removed and properly disposed of before an MRI procedure. Following an MRI procedure, another fentanyl ITS device can then be applied.

RFID devices are located throughout hospitals. They are commonly used to track medications, patients, nurses, doctors, and equipment in real time. The FDA has set up a program to work with manufacturers of potentially susceptible medical devices to test their products for any adverse effects from RFID exposures. Therefore, it is critical that any device (including PCA pumps) be compatible with RFID devices; the fentanyl ITS system met all those standards. While the RFID devices are typically situated at some distance from a patient, the current study evaluated the effect of exposure with direct contact to the controller to encompass the most extreme possibility. For all test conditions, the system operated normally in all operating modes including the Ready or Dose Modes. This is especially important as the use of RFID devices in hospitals continues to expand.

It is important to note that this study was conducted on the second-generation fentanyl ITS which is the currently marketed system.

With the first-generation system, it was determined that the co-packaging of the electronics within the same primary packaging as the hydrogels exposed the electronics to extreme humidity that could potentially damage the electronics and potentially result in self-initiation of the system. The challenges to the first system were unrelated to radiation or RFID. The second-generation system was designed to fully address the earlier issues by separating the hydrogels in the drug unit from the electronic circuit of the controller during manufacture and storage, which removed the primary cause of corrosion and thereby improved reliability [2].

A limitation of this study was that it was conducted in the laboratory versus a hospital setting such that the laboratory data has to be extrapolated to the clinical setting. The study was designed to test the system under conditions that would translate to a hospital setting. In addition, the study tested extreme circumstances to demonstrate a large margin of safety. Specifically, the system was tested with radiation levels that were 25× higher than the typical X-ray and 10× higher than the typical CT scan. For RFID, the system and the RFID were positioned adjacently, while in the hospital some distance would exist. It would not be possible to conduct a study under such conditions utilizing patients, and overall these results inform conditions of use in clinical practice. It is also important to note that this system has been tested in a comprehensive, multi-study Phase 3 clinical program that showed the system to be efficacious with a safety profile consistent with the administration of all opioid medications. [3–9] Collectively, the clinical and laboratory data provide a set of data that demonstrates the safe and effective use of the fentanyl ITS system.

CONCLUSION

In conclusion, the results of this study support the conclusion that the fentanyl ITS can be used safely and effectively in hospitals utilizing the RFID technology at any distance. Also, the fentanyl ITS is not affected by exposure to radiation levels well beyond those typical of diagnostic X-rays or CT scans. These results should provide added confidence to clinicians that the fentanyl ITS system can be used during X-rays and CT scans as well as in the proximity of RFID devices.

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