Original Article

Chemical Degradation of Intravenous Chemotherapy Agents and Opioids by a Novel Instrument

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Abstract

Purpose: To assess chemical degradation of various liquid chemotherapy and opioid drugs in the novel RxDestruct™ instrument. **Methods:** Intravenous (IV) drug solutions for chemotherapy and pain management were prepared using 0.9% normal saline in Excel® bags to a final volume of 500 mL. We investigated duplicate IV solutions of methotrexate (0.1 mg/mL), etoposide (0.4 mg/mL), doxorubicin (0.25 mg/mL), cladribine (12.4 µg/mL), fentanyl (1.0 µg/mL), and hydromorphone (12.0 µg/mL) in this study. Solutions were poured into an automated instrument to undergo pulsatile chemical treatment (Fenton reactions) for 20 minutes, and then discharged from the instrument through a waste outlet. Extent of intact drug degradation was determined by measuring concentrations of drugs before entry into the instrument and after chemical treatment in the filtrate using high-performance liquid-chromatography with ultraviolet detection (HPLC-UV). **Results:** Following chemical reactions (Fenton processes) in the automated instrument, infusion solutions containing methotrexate, etoposide, doxorubicin, and cladribine had levels below the HPLC-UV limit of quantification (LOQ), indicating $<$50 ppb of each. This equated to $>$99.5%, 99.99%, 99.9%, and 99.8% intact drug loss, respectively. Likewise, processed samples of fentanyl and hydromorphone contained levels below the LOQ (78 and 98 ng/mL, respectively), indicating extensive degradation ($>$92.2% and 99.2% intact drug loss, respectively). **Conclusion:** The novel instrument was capable of degrading intact chemotherapy and opioid drugs prepared in infusion solutions to undetectable quantities by HPLC-UV. RxDestruct™ is a possible alternative for disposal of aqueous medication waste.

Keywords
analgesics, drug stability, antineoplastics, intravenous therapy, oncology, medication process, dispensing

Introduction

Unused medicines, including controlled substances and hazardous chemotherapy agents, represent a major source of wastage in healthcare systems around the world.[1] The WHO (World Health Organization) reported 0.2 to 0.5 kg of total waste generated per hospital bed per day, of which 3% was attributable to drug wastage. Today, a common (and Environmental Protection Agency (EPA)-approved) medication waste management practice is incineration followed by landfilling, but this has notable disadvantages. For instance, incineration and disposing of medication waste is a costly endeavor that can significantly affect pharmacy budgets.[2,3] Waste stream, including pharmaceutical waste, that is generated each year from US hospitals is significant, reaching almost 5.9 billion tons of waste per year.[2,3] It is estimated that proper, safe disposal of this waste through incineration and landfilling costs into the billions each year.[2,3] Furthermore, incineration of pharmaceutical waste can produce toxic air emission (e.g., ozone depleting agents, and other hazardous by-products) that pollute environmental air.[4] Drugs can also leach into the environment from landfills.[5] Mixing psychoactive drugs (e.g., opioids) with cat litter or coffee grounds, to be disposed in regular garbage, is not always effective since drugs can still be extracted.[4] Thus, this method cannot effectively prevent drug theft and abuse.[4] The current health care system is experiencing an overwhelming epidemic of opioid diversion, misuse, and abuse, part of which is due to improper disposal of unused opioid medications.[6]

Also concerning is that trace levels of pharmaceuticals have been detected in sewage treatment plant effluents, surface waters, seawaters, groundwater, and drinking waters

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in many countries including the US.[7] There are several ways that pharmaceuticals make their way into the environment. By far the biggest contribution comes from drugs administered to humans and animals that are eventually excreted into the urine or feces. But, the improper disposal of drugs also makes a contribution, such as when leftover drugs are thrown into the garbage or flushed down the sink or toilet.[8] In a chemical analysis of US wastewater effluent samples from major urbanized areas, 56 different pharmaceuticals (and some drug metabolites) were found, including various diuretics, antidepressants, anti-convulsants, β-blockers, angiotensin-2-receptor blockers (ARBs), and several others.[8] As an example, among the 50 treatment facilities tested, hydrochlorothiazde was found in all samples and metoprolol, atenolol, and carbamazepine were found in over 90% of the samples.[8] The presence of pharmaceuticals in the environment also raises concerns of, to name a few, greater anti-microbial resistance in humans (due to accumulation of antibiotics), reproduction changes in humans and aquatic life (due to hormones), and behavioral changes (due to psychotropics).[9,10]

Hence, a safer, convenient, effective, and less expensive drug disposal method is critically required. Ozonation and advanced oxidation processes are possible alternatives to thermal degradation for destroying aqueous pharmaceuticals.[11] Among the advanced oxidation processes are Fenton-type reactions, which generate destructive hydroxyl radicals from the mixture of iron (ferrous) salts and hydrogen peroxide that ultimately breakdown molecular structures.[11,12] Fenton-type processes have been shown in the laboratory to completely degrade solutions of anti-neoplastic agents: cyclophosphamide,[13] ifosfamide,[13] melphalan,[13] thiotepa,[14] asparaginase,[14] and anthracyclines.[15] Studies have also demonstrated that solutions of anti-cancer pharmaceuticals degraded by the Fenton reaction contain non-mutagenic residues.[13]

However, potential utilization of the Fenton reaction in destroying pharmaceutical waste in a clinical operational setting is poorly studied. With this in mind, a novel investigational instrument (RxDestruct™) was engineered and developed for real-world benchtop application—which ultimately discharges an effluent that can be poured down a drain. One potential application of the instrument is to degrade liquid pharmaceuticals (e.g., anti-cancer agents, opioids), however its effectiveness in doing so is currently unknown.

Therefore, the primary objective of this study was to determine the extent of chemical degradation of four commonly wasted liquid chemotherapy drugs (methotrexate, etoposide, doxorubicin, and cladribine) at our hospital, and extent of degradation for two highly prescribed IV-administered opioids (fentanyl and hydromorphone).

Methods

Sample Preparations

Authentic standards of methotrexate, etoposide, doxorubicin, and cladribine were acquired from Selleck Chemicals (Houston, TX). Reference standards of fentanyl and hydromorphone were purchased from USP (Rockville, MD). All solvents were of HPLC grade or higher purity and purchased from Fisher Scientific (Fair Lawn, NJ). Water for HPLC analysis was prepared by a Milli-Q ultrapure water purification system (Millipore; Bedford, MA).

To select the liquid anti-cancer drugs used in the present study, a brief survey of our hospital records was conducted to identify the drugs most wasted during a 3-month time period—categorized based on quantity of drug wasted and associated expenses. The following drugs were selected: Methotrexate Injection,[a] Etoposide Injection,[b] Doxorubicin Injection,[c] and Cladribine Injection.[d] Opioids included Fentanyl citrate Injection[e] and Hydromorphone Injection.[f] All drugs were obtained internally from the hospital pharmacy. Drugs were diluted with 0.9% normal saline and prepared in Excel® bags (in duplicate) to a final volume of 500 mL. Final concentrations of drugs in the tested IV solutions was calculated based on the higher range of recommended daily doses by the individual drug manufacturer's package insert, assuming a normalized adult patient body surface area of 1.75 m^2 when appropriate. Final concentrations for methotrexate, etoposide, doxorubicin, cladribine, fentanyl, and hydromorphone were 0.1 mg/mL, 0.4 mg/mL, 0.25 mg/mL, 12.4 µg/mL, 1.0 µg/mL, and 12 µg/mL, respectively. All sample preparations were conducted in a Class 100 environment in a biological safety cabinet.

HPLC-UV Assays

The magnitude of degradation of anti-cancer drugs and opioids was monitored by the disappearance of the parent (intact) compound after treatment in the instrument using high-performance liquid chromatography with ultraviolet detection (HPLC-UV). All assays were validated to be stability indicating on a Waters 2695 Separations Module[g] following our previous methods.[16–21] Further information on the individual HPLC-UV methods follows:

Methotrexate assay. Parent methotrexate was separated using a Phenomenex Synergy MAX-RP (Torrance, CA) C12 analytical column (150 × 4.6 mm, 4 µM, 80°) maintained at 25°C. A Phenomenex guard cartridge of similar material protected the column. The photodiode array detector (PDA) was set at 304 nm. Mobile phase consisted of the following mixture (85:15): 100 mM disodium hydrogen phosphate buffer (pH 6.0) and acetonitrile. Mobile phase was delivered isocratically at 1.0 mL/min over 6 minutes following each injection (10 µL). Under these conditions, methotrexate eluted at approximately 3.7 minutes.

Etoposide assay. Intact etoposide was separated using a Phenomenex Synergy MAX-RP HPLC column (150 × 4.6 mm, 4 µM, 80°) stored at 25°C. The column was protected by a Phenomenex guard cartridge of similar material. The photodiode

array detector (PDA) was set at 206 nm. Mobile phase consisted of the following mixture (65:35): 25 mM potassium dihydrogen phosphate buffer (pH 3.25) and acetonitrile. Mobile phase was delivered isocratically at 1.0 mL/min over 6.5 minutes following each injection (10 µL). Under these conditions, etoposide eluted at approximately 4.4 minutes.

Doxorubicin assay. Separation of parent doxorubicin was achieved using a Phenomenex Synergy MAX-RP HPLC column (150 × 4.6 mm, 4 µM, 80°) maintained at 25°C. The column was protected by a Phenomenex guard cartridge of similar material. The photodiode array detector (PDA) was set at 233 nm. Mobile phase consisted of the following mixture (74.5:25.5): 25 mM potassium dihydrogen phosphate buffer (pH 3.25) and acetonitrile, respectively. Isocratic delivery of mobile phase was accomplished by 6 minutes using a flow rate of 1.2 mL/min. The injection volume was 10 µL. Under these conditions, etoposide eluted at approximately 4.6 minutes.

Cladribine assay. Separation of cladribine was achieved using a Phenomenex Synergy MAX-RP HPLC column (150 × 4.6 mm, 4 µM, 80°) maintained at 25°C and protected by a Phenomenex guard cartridge of similar material. The photodiode array detector (PDA) was set at 264 nm for detection of analyte. Mobile phase consisted of the following mixture (94:6): 37 mM ammonium phosphate dissolved in 10% acetonitrile, and acetonitrile, respectively. Mobile phase was delivered isocratically at 0.9 mL/min over 8 minutes following each injection (10 µL). Under these conditions, cladribine eluted at approximately 3.8 minutes.

Fentanyl assay. Intact fentanyl was separated using a Waters Symmetry (Milford, MA) C18 analytical column (150 × 3.9 mm, 5 µM) maintained at 35°C. The column was protected by a Phenomenex C18 guard cartridge. Analyte was detected at 210 nm. Mobile phase contained a 60:40 mixture of 25 mM potassium dihydrogen phosphate buffer (pH 3.1; 60%), and a 50:50 mixture of acetonitrile and methanol (40%). Mobile phase was delivered isocratically at 1.0 mL/min over 10 minutes following each injection (10 µL). Under these reversed phase conditions, fentanyl eluted at approximately 3.6 minutes.

Hydromorphone assay. Separation of intact hydromorphone was achieved using a Waters XTerra C18 reversed phase column (150 × 4.6 mm, 3.5 µM) maintained at 25°C. The column was protected by a Phenomenex C18 guard cartridge. PDA detection was conducted at 210 nm. Mobile phase consisted of the following mixture (90:10): 25 mM potassium dihydrogen phosphate buffer (pH 3.5) and acetonitrile, respectively. Mobile phase was delivered isocratically at 0.9 mL/min over 6 minutes following each injection (10 µL). As such, hydromorphone eluted at approximately 4 minutes.

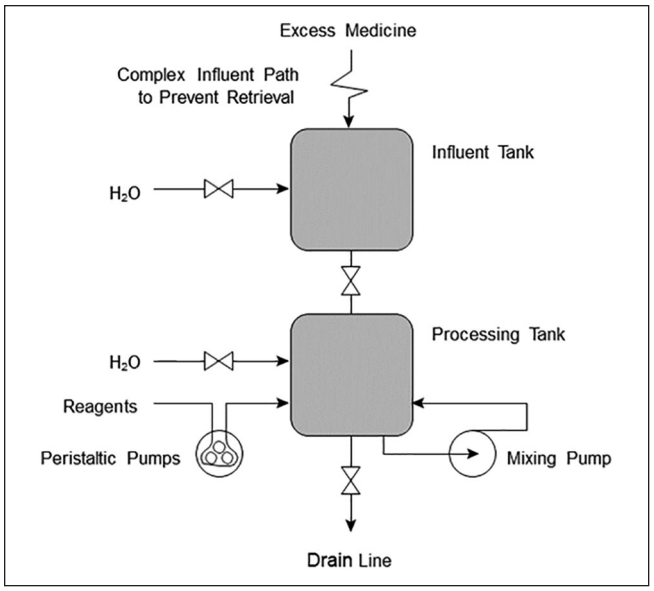

Figure 1. Schematic of the inner workings of the RxDestruct™ instrument.

Chemical Destruction Experiments

The flow diagram and schematics of RxDestruct™ is included in Figure 1. After preparation of test drug in the IV bag, a small aliquot (0.5 mL) was withdrawn and the concentration promptly measured by HPLC-UV as described above (this served as the "before treatment" sample). The remaining solution in the IV bag was poured into an inlet valve that drains directly into the influent tank (Figure 1). The IV solution is immediately diluted with 500 mL of distilled water in the influent tank. Upon mixing, the solution was pumped into the processing tank (Figure 1) in which a peristaltic pump delivers three sequential pulses of Fenton's reagent (mixture of ferrous sulfate and hydrogen peroxide in water), with each pulse delivered in approximately 6 minutes intervals. The final eluent was pumped out of the instrument (drain line) into a large glass beaker and was brownish-yellow in color. The total time for treatment in the instrument was less than 20 minutes. A 10 mL aliquot of eluent was filtered through a 17 mm Phenex (Phenomenex) syringe filter (0.45 µm porosity) to yield a clear solution (this served as the "after" treatment sample). The presence (concentration) of compounds in filtrate was determined by HPLC-UV.

Results

HPLC Assays

Good system precision was obtained where intra-sample precision, expressed as Percentage Relative Standard Deviation (%RSD), was ≤5% for all analytical methods. The intra-day and inter-day coefficients of variations were ≤8.5% for all assays. For methotrexate, the assay was linear from 0.05 to

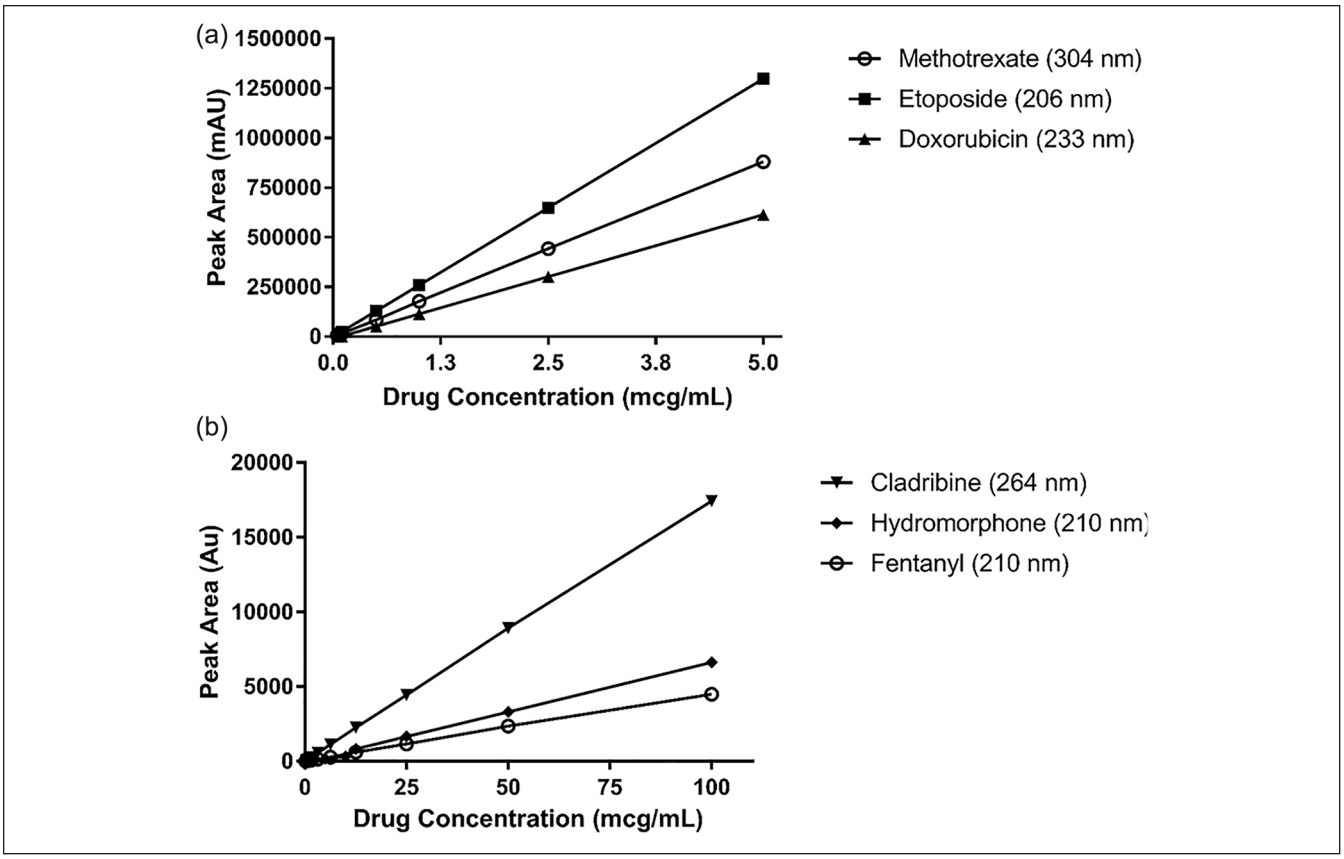

Figure 2. (a) Calibration curves following injection of series of known authentic standards for methotrexate, etoposide, and doxorubicin. Concentrations were determined by the individual HPLC-UV assays described in the text. Wavelengths for detection are noted in each figure legend. The assays were linear from 0.05 to 5.0 µg/mL with a correlation coefficient (R^2) > 0.997 for all three anti-cancer drugs. (b) Calibration curves for cladribine and opioids. Linearity (all $R^2 > 0.999$) was achieved from 0.05 to 100 µg/mL, 0.078 to 100 µg/mL, and 0.098 to 100 µg/mL, for cladribine, fentanyl, and hydromorphone, respectively.

5.0 µg/mL ($R^2 > 0.999$) and the limit of quantification (LOQ) was 50 ng/mL, while the etoposide assay was linear from 0.05 to 5.0 µg/mL ($R^2 > 0.997$) with a LOQ of 50 ng/mL. The calibration curves for doxorubicin and cladribine were linear from 0.05 to 5.0 µg/mL ($R^2 > 0.998$) and 0.05 to 100 µg/mL ($R^2 > 0.999$), respectively; and the LOQ was 50 ng/mL for both. For the opioids, linearity was observed from 0.078 to 100 µg/mL ($R^2 > 0.999$) and from 0.098 to 100 µg/mL ($R^2 > 0.999$) for fentanyl and hydromorphone, respectively. The LOQ for fentanyl and hydromorphone was 78 and 98 ng/mL, respectively. A compilation of standard curves is included in Figure 2a (methotrexate, etoposide, and doxorubicin) and in Figure 2b (cladribine, fentanyl, and hydromorphone).

Chemical Destruction

After treatment in the RxDestruct™ instrument, there was complete disappearance of parent drug in all of the samples. Therefore, the total extent of degradation of each sample was limited to the individual HPLC assay LOQ. This means that in chemically treated samples of methotrexate, etoposide, doxorubicin, and cladribine there was less than 50 ng/ml (50 ppb) of drug remaining. For fentanyl and hydromorphone there was less than 75 ng/mL (75 ppb) and 98 ng/mL (98 ppb) remaining, respectively.

Representative HPLC-UV stacked chromatograms prior to and after chemical treatment in the instrument are included in Figure 3 for methotrexate (3a), etoposide (3b), doxorubicin (3c), and cladribine (3d). The representative chromatograms for fentanyl and hydromorphone are shown in Figure 4a and b, respectively.

Discussion

Proper and safe disposal of hospital pharmaceutical waste in the US is estimated to cost billions of dollars per year, representing a significant economic burden to the US health care system.[2,3] A major source of drug wastage during hospital oncology care is injectable medications. However, beyond incineration and landfilling there are few options for pharmacies to efficiently discard liquid oncology agents in the

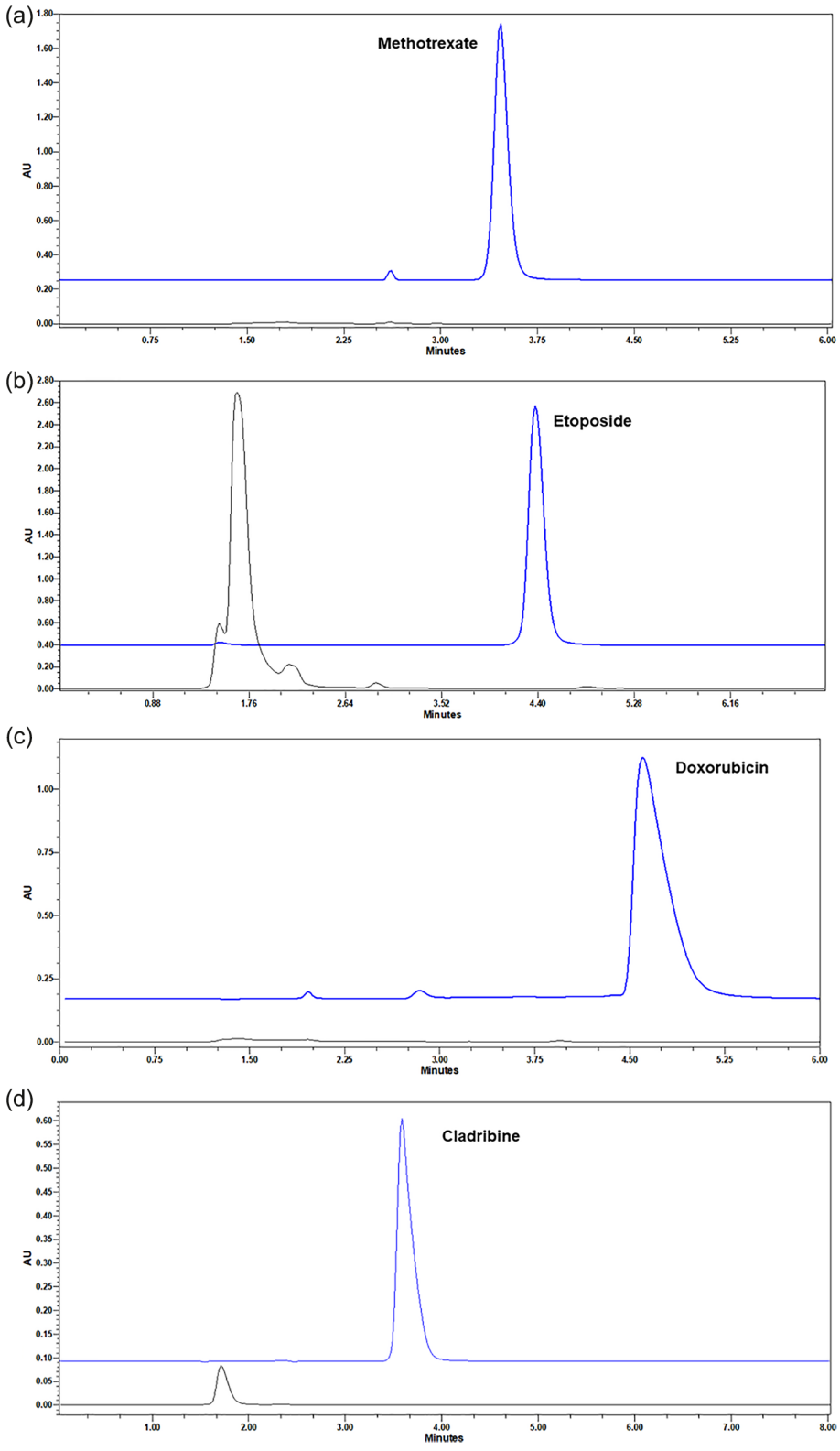

Figure 3. HPLC-UV Chromatograms from before (blue tracing) and after treatment (black tracing) in the RxDestruct™ instrument. Drugs significantly degraded following pulsatile delivery of Fenton reagents were methotrexate (a), etoposide (b), doxorubicin (c), and cladribine (d). Concentrations of these medications diluted in 0.9% NS before treatment were 100, 400, 250, and 12.4 µg/mL for methotrexate, etoposide, doxorubicin, and cladribine, respectively.

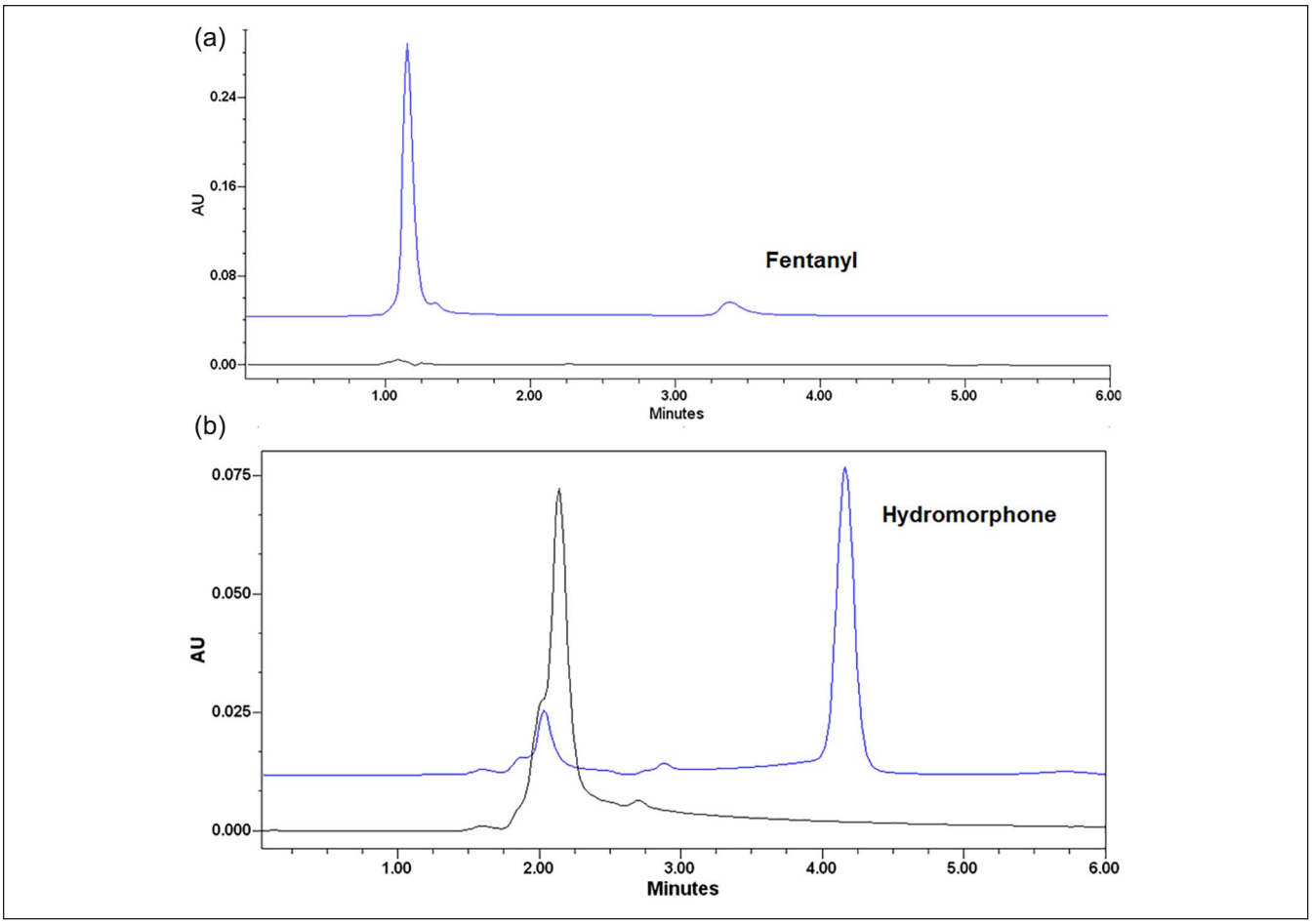

Figure 4. Representative HPLC-UV chromatograms of intravenous opioid agents prepared in 0.9% NS before (blue tracing) and after processing (black tracing) in the RxDestruct™ instrument. Drugs appreciably degraded by the automated Fenton reactions were fentanyl (a) and hydromorphone (b) in concentrations of 1.0 and 12 µg/mL, respectively, prior to treatment.

real-time health care practice setting. Thus, alternative methods of drug disposal with published testing results are of great interest. Advanced oxidation processes, such as the Fenton reaction, are promising strategies to degrade pharmaceutical waste. However, few studies have reported the feasibility of utilizing these advanced oxidation processes in an operational setting where most drug disposal occurs. Furthermore, the studies that have applied Fenton chemical degradation processes have focused mainly on treating wastewater eluent.[22]

In this study, we have shown that a novel instrument is significantly able to degrade liquid oncology drugs (specifically methotrexate, etoposide, doxorubicin, and cladribine) to undetectable levels as analyzed by HPLC-UV assays. Specifically, greater than 95% intact chemotherapy drug was degraded in the instrument, suggesting that RxDestruct™ has promise in disposing of liquid oncology drugs without the need for conventional drug disposal methods.

According to the CDC, there were more than 400,000 opioid-related deaths in the United States from 1999 to 2017, with over 70,000 deaths in 2017 alone. Unused and improperly stored opioid medications are risk factors for opioid misuse, abuse, and diversion.[23] To combat these issues, several drug disposal products have been marketed, such as RxDestroyer™, DisposeRx®, Drug Buster®, and NarcX®. The disposal mechanisms of these products relies on drug adsorption to inert materials such as charcoal or clay, and/or sequestration by viscous gels, and/or mixing with undesirable chemicals. The "reacted" drug product is recommended for disposal in the garbage (trash), and in some cases incineration.[23] A recent report by the Community Environmental Health Strategies, LLC noted that there are numerous limitations of these commercial products.[24] Some products do not publish testing results or those that have provide only limited details with no clear verifications.[24] Several products have limited disclosure of active ingredients, and even some claim that the treated drug can be readily extracted by washes with water and other solvents.[24]

In the present study, we have demonstrated that the instrument efficiently degraded two commonly used intravenous opioid agents—fentanyl and hydromorphone. The present opioid data adds to preliminary studies conducted at

Campbell University, College of Pharmacy and Health Sciences in the Pharmaceutical Education and Research Center (PERC). There, solutions of fentanyl and hydromorphone were degraded to "undetectable" quantities in the instrument, but the LOQ of these drugs was not elaborated.[25] Aliquots of fentanyl and hydromorphone samples processed in our laboratory were additionally sent to an external bioanalytical laboratory (ARL BioPharma Inc., Oklahoma City, OK, USA) for more sensitive mass spectroscopic analysis. LC-MS/MS analysis also showed no detectable peaks in processed samples, indicating almost complete degradation (>99.92% intact drug loss) based on the drug's LOQs.[25]

Due to the small dimensions of the instrument, it is potentially useful in many places pharmaceuticals are being administered or dispensed, such as in hospitals, surgical centers, doctors' offices, pharmacies, etc. Implementation of the instrument may reduce opioid diversion, misuse, and abuse, which is of paramount interest in today's ever-pressing opioid epidemic. Several barriers to implementation require mention. Health care workers responsible for pouring chemotherapy agents into RxDestruct™ should receive proper training in handling controlled substances and hazardous chemicals, as well as on the use of appropriate personal protective equipment (PPE). In addition, the time and effort required of the instrument operator should be thoughtfully included into budgetary decisions. Although we have tested an array of chemicals with varying chemical structures, future studies could examine the instrument's effectiveness in degrading other pharmaceuticals of interest.

Conclusion

A novel instrument (RxDestruct™) was capable of degrading IV infusion solutions of various chemotherapy (methotrexate, etoposide, doxorubicin, and cladribine) and opioid medications (fentanyl and hydromorphone) to undetectable quantities as measured by HPLC-UV before and after treatment with Fenton reagents (>99.5% loss for chemotherapy drugs and >99.2% loss for opioids). The novel instrument is a promising alternative to disposing of intravenous medication waste in a hospital pharmacy or clinical operational setting.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Mr. Macdonell is CEO of Clear River Enviro Inc.

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Notes

a Methotrexate Injection, USP, 25 mg/mL, Hospira Inc., Lake Forest IL, Lot no. C034457AC.
b Etoposide Injection, USP, 20 mg/mL, Teva Parenteral Medicines Inc., Irvine, CA, Lot no. 31321165B.
c Doxorubicin HCl Injection, USP, 2 mg/mL, Pfizer Injectables, New York, NY, Lot no. N11660.
d Cladribine Injection, USP, 1 mg/mL, Fresenius Kabi, Lake Zurich, IL, Lot no. 6113030.
e Fentanyl citrate Injection, USP, 50 µg/mL West-Ward, Eatonville, NJ.
f Hydromorphone Injection, USP, 2 mg/mL, West-Ward, Eatonville, NF, Lot no. 087375.
g Waters 2695 Separations Module (Milford, MA) coupled to a Waters 996 photodiode array (PDA) detector. System was controlled by Waters Empower II software.

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