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Feasibility of 48-Hour Continuous Subcutaneous Infusions: Insights from Seven NHS Acute Hospitals

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Abstract

Continuous subcutaneous infusions (CSCIs) are widely employed in the United Kingdom to deliver medications for symptom management when oral administration is not feasible. Currently, CSCIs are generally administered over a 24-hour period, based on available safety data. Extending CSCI administration to 48 hours could offer potential advantages for patient care and healthcare resource utilization. This service evaluation aimed to determine how frequently CSCI prescriptions are modified in NHS acute hospital settings. Pharmacists and palliative care team members at seven acute NHS hospitals collected anonymized prescription information for CSCIs containing two or more drugs. Data recorded daily included drug combinations, dosages, diluents, and compatibility, with a minimum observation period of 2 days and a maximum of 7 days. Across the seven hospitals, 1301 prescriptions from 288 patients were recorded, representing 584 unique drug combinations. Of these, 91% (n = 533) contained an opioid. The ten most frequently prescribed drug combinations accounted for 37% of all combinations. The median duration for which a CSCI prescription remained unchanged at all sites was 2 days. The findings indicate that administering medications via CSCI over 48 hours could be feasible. Prior to conducting a clinical feasibility study, further work is required, including pharmacoeconomic evaluation, detailed chemical and microbiological stability testing, and exploration of the acceptability of 48-hour infusions among clinical staff, patients, and families.

Keywords: Palliative care, Continuous subcutaneous infusion, CSCI, NHS acute hospitals

Introduction

Recent studies suggest that up to one-third of patients in UK District General Hospitals may be in their final year of life [1]. With the annual number of deaths projected to rise from 468,875 in 2014 to 561,000 by 2035/36 [2], delivering effective end-of-life care is becoming increasingly challenging. Most patients prefer to die at home [3, 4], which places additional pressure on NHS services to support individuals wishing to remain in familiar surroundings [5, 6].

Financial constraints further complicate this issue, as NHS England projected a £22 billion savings target by 2020 [7]. These pressures necessitate innovative approaches to care delivery that maximize patient outcomes while efficiently utilizing limited resources [8]. Workforce shortages, including unfilled medical and nursing positions [9] and a decreasing number of qualified district nurses responsible for home care [10], highlight the urgent need for changes to maintain high-quality treatment.

Continuous subcutaneous infusions (CSCIs) are an established method for administering multiple medications when oral intake is not possible [11, 12]. Current chemical and microbiological stability data limit the duration of these infusions to 24 hours [13]. However, a pilot study at a UK teaching hospital found that in 72% of cases (n

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= 38), the medication regimen remained unchanged during the first 48 hours of infusion [14]. This observation indicates that, for patients with stable symptom control needs, extending the infusion period to 48 hours may be feasible. Such a practice could enhance patient autonomy, allow clinicians to dedicate more time to direct care, and optimize healthcare resource utilization.

This evaluation aimed to examine how frequently CSCI prescriptions are modified across NHS acute hospitals to identify potential candidates for 48-hour infusions. Secondary objectives included determining the most commonly prescribed drugs and combinations, and analyzing dosing patterns.

Materials and Methods

Participation was solicited through the UK Palliative Care Pharmacist Network, resulting in 11 hospitals expressing interest. Pharmacists or palliative care team members at each site identified patients prescribed CSCIs containing two or more drugs between July and December 2016.

A designated pharmacist at each hospital entered anonymized prescription data into a secure electronic database managed by the Liverpool Cancer Trials Unit. The study targeted at least 50 patients per hospital. Patients who died or were discharged before 48 hours were excluded from analysis.

For each patient, healthcare professionals recorded daily information on drug combinations, dosages, diluents, and compatibility over a period of 2 to 7 days. Data collection ceased if the CSCI was discontinued before 7 days or at the end of the 7-day period.

The primary outcome was the duration that CSCI prescriptions remained unchanged. Descriptive statistics were calculated, presenting categorical variables as counts and continuous variables as medians with interquartile ranges. Regression models were used to examine differences in unchanged prescription duration across sites and by the most frequently used drug combinations, accounting for variability between patients and hospitals.

Results and Discussion

Of the 11 hospitals expressing interest, one declined, two did not respond, and one did not secure Research and Development approval. The participating hospitals were located across the North of England, including three in Merseyside, and one each in Lancashire, Greater Manchester, and South Yorkshire.

At the time of data analysis, 1301 CSCI prescriptions had been recorded (61 entries excluded due to errors), representing 584 unique drug combinations. Water for Injections was used as a diluent in 766 cases (58.9%), 0.9% sodium chloride in 528 cases (40.6%), and no diluent was recorded in 7 cases.

Frequency of prescription changes

Analysis of the duration for which each CSCI combination remained unchanged is presented in **Table 1**, including data from 288 patients and 582 combinations (two combinations were excluded due to incomplete records). Overall, 45% of combinations (262/582) were modified within the first 48 hours. A further 38% (221/582) remained unchanged beyond 48 hours but were altered before 72 hours, while 17% (99/582) persisted without modification for more than three days.

When examining prescriptions over a standard five-day week (Monday to Friday), 36.7% (214/582) remained unaltered for at least 48 hours. Expanding the analysis to include a seven-day week, which accounted for weekends, this proportion increased to 55% (320/582). Across all sites, the median duration for an unchanged CSCI prescription was 2 days. Notably, at sites 3, 5, and 7, the median duration was slightly shorter, remaining under 2 days.

Table 1. Overview of CSCI prescribing across all sites.

Site	No. of Patients	No. of CSCI Combinations Recorded	No. of CSCIs Ran Unchanged for 1 Day	No. of CSCIs Ran Unchanged for 2–3 Days	No. of CSCIs Ran Unchanged for 3+ Days	No. of CSCIs Ran for 2+ Consecutive Days (Excluding Saturday and Sunday)	Median Duration of Unchanged CSCI Prescription (Days, IQR)
1	83	151	56	57	38	41	2 (1, 4)
2	64	128	48	55	25	28	2 (1, 3)
3	11	20	10	8	2	2	1.5 (1, 2.75)
4	26	53	20	25	8	8	2 (1, 3)
5	34	71	39	26	6	9	1 (1, 2)
6	21	35	12	13	10	9	2 (1, 4)
7	49	124	77	37	10	9	1 (1, 2)

Regression modeling was conducted to determine whether the duration of CSCI administration was influenced by either the treatment site or the specific drugs prescribed. Model estimates for the effects of treatment site are summarized in **Table 2**. Compared with site 1, sites 3, 5, and 7 showed significantly shorter durations of CSCI administration, indicating that prescriptions at these locations were generally changed more quickly. Site 4 approached statistical significance at the 5% level. In contrast, the analysis found no evidence that the type of drug prescribed had a significant impact on the length of time a CSCI was administered.

Table 2. Results of the mixed log-logistic model to evaluate factors associated with administration time.

	Estimate	Standard Error	z value	Pr(>|z|)
Intercept	1.012	0.098	10.290	0.000
Site 1	–	–	–	–
Site 2	−0.118	0.090	−1.316	0.188
Site 3	−0.372	0.173	−2.152	0.031
Site 4	−0.235	0.123	−1.907	0.057
Site 5	−0.407	0.113	−3.607	0.000
Site 6	0.003	0.135	0.022	0.982
Site 7	−0.437	0.096	−4.549	0.000

Drugs used in CSCIs

Table 3 summarizes the frequency of each drug prescribed, along with descriptive statistics for dosage, including mean, median, range, and interquartile range. Analysis revealed that the four most frequently used medications—midazolam hydrochloride, oxycodone hydrochloride, levomepromazine hydrochloride, and morphine sulphate—comprised 983 of 1,605 prescriptions, representing 61% of all drugs administered.

Table 3. Frequency and dose range of drugs prescribed in CSCI combinations recorded.

Drug	UK Licensing Status for SC Infusion	Frequency	Mean Dose (mg)	Median Dose (mg)	Dose Range (mg)	IQR (mg)
Midazolam hydrochloride	Unlicensed	309	11.63	10	(2.5, 60)	(5, 12.5)
Oxycodone hydrochloride	Licensed	230	21.09	15	(2.5, 150)	(7.5, 25)
Levomepromazine hydrochloride	Licensed	225	13.77	6.25	(6.2, 150)	(6.2, 12.5)
Morphine sulphate	Unlicensed	219	19.14	10	(2.5, 190)	(7.5, 20)
Glycopyrronium bromide	Unlicensed	120	1.35	1.2	(0.4, 2.4)	(0.6, 2)
Hyoscine butylbromide	Unlicensed	105	89.9	60	(20, 240)	(60, 120)
Alfentanil hydrochloride	Unlicensed	82	1.8	1.12	(0.2, 12.5)	(0.6, 2)
Haloperidol lactate	Unlicensed	66	2.7	2.5	(0.5, 10)	(1.5, 3)
Cyclizine lactate	Unlicensed	62	150	150	(150, 150)	(150, 150)
Clonazepam	Unlicensed	57	1.18	1	(0.1, 6)	(0.2, 2)
Metoclopramide hydrochloride	Unlicensed	46	36.52	30	(15, 90)	(30, 40)
Ondansetron hydrochloride	Unlicensed	33	15.52	12	(8, 36)	(12, 16)
Ketamine hydrochloride	Unlicensed	13	171.15	150	(100, 300)	(125, 200)
Octreotide acetate	Unlicensed	11	0.65	0.6	(0.6, 0.9)	(0.6, 0.6)
Hyoscine hydrobromide	Unlicensed	11	1.47	1.2	(1.2, 2.4)	(1.2, 1.5)
Dexamethasone sodium phosphate	Unlicensed	10	0.98	1	(1, 1)	(1, 1)
Levetiracetam	Unlicensed	2	375	375	(250, 500)	(312.5, 437.5)

Furosemide	Unlicensed	2	200	200	(200, 200)	(200, 200)
Diamorphine hydrochloride	Licensed	2	7.5	7.5	(5, 10)	(6.2, 8.8)

Across the seven sites, 584 CSCI prescriptions represented 128 unique drug combinations. The distribution of the number of drugs per combination was as follows: two-drug combinations accounted for 251 of 584 prescriptions (43%), three-drug combinations for 232 (40%), four-drug combinations for 98 (17%), and five-drug combinations for 3 (<1%). The 31 most frequently prescribed combinations are detailed in **Table 4**.

Table 4. Top 31 combinations present in 1301 recorded CSCI prescriptions.

Drug 1	Drug 2	Drug 3	Drug 4	Frequency
Morphine sulphate	Midazolam hydrochloride	-	-	40[a]
Oxycodone hydrochloride	Midazolam hydrochloride	-	-	35
Morphine sulphate	Glycopyrronium bromide	Levomepromazine hydrochloride	Midazolam hydrochloride	25
Morphine sulphate	Levomepromazine hydrochloride	Midazolam hydrochloride	-	22
Oxycodone hydrochloride	Hyoscine butylbromide	Midazolam hydrochloride	-	21
Morphine sulphate	Glycopyrronium bromide	Midazolam hydrochloride	-	19
Oxycodone hydrochloride	Levomepromazine hydrochloride	Midazolam hydrochloride	-	14
Alfentanil hydrochloride	Levomepromazine hydrochloride	Midazolam hydrochloride	-	13[a]
Oxycodone hydrochloride	Glycopyrronium bromide	Levomepromazine hydrochloride	Midazolam hydrochloride	13
Morphine sulphate	Levomepromazine hydrochloride	Midazolam hydrochloride	-	13[a]
Oxycodone hydrochloride	Metoclopramide hydrochloride	-	-	10
Oxycodone hydrochloride	Clonazepam	Haloperidol lactate	-	10
Oxycodone hydrochloride	Clonazepam	-	-	10
Oxycodone hydrochloride	Cyclizine lactate	-	-	10
Alfentanil hydrochloride	Glycopyrronium bromide	Levomepromazine hydrochloride	Midazolam hydrochloride	10
Morphine sulphate	Cyclizine lactate	-	-	9
Oxycodone hydrochloride	Hyoscine butylbromide	Haloperidol lactate	-	8
Morphine sulphate	Hyoscine butylbromide	Midazolam hydrochloride	-	8
Morphine sulphate	Metoclopramide hydrochloride	-	-	7[a]
Oxycodone hydrochloride	Haloperidol lactate	Midazolam hydrochloride	-	7
Alfentanil hydrochloride	Levomepromazine hydrochloride	Midazolam hydrochloride	-	7
Hyoscine butylbromide	Levomepromazine hydrochloride	-	-	7
Oxycodone hydrochloride	Glycopyrronium bromide	Midazolam hydrochloride	-	7
Glycopyrronium bromide	Midazolam hydrochloride	-	-	7
Oxycodone hydrochloride	Cyclizine lactate	Haloperidol lactate	-	6

Alfentanil hydrochloride	Glycopyrronium bromide	Midazolam hydrochloride	-	6
Alfentanil hydrochloride	Hyoscine butylbromide	Levomepromazine hydrochloride	Midazolam hydrochloride	5
Morphine sulphate	Hyoscine butylbromide	Levomepromazine hydrochloride	Midazolam hydrochloride	5
Oxycodone hydrochloride	Hyoscine butylbromide	Levomepromazine hydrochloride	Midazolam hydrochloride	5
Oxycodone hydrochloride	Hyoscine butylbromide	Levomepromazine hydrochloride	-	5

[a]indicates combinations known to have been analysed for 48-h compatibility and stability at clinically relevant doses

Opioid use and drug compatibility

Opioids were included in 91% of prescriptions (n = 533), with morphine sulphate present in five of the six most frequently prescribed combinations. All six of these common combinations also contained midazolam hydrochloride. Laboratory-tested chemical compatibility and stability data at clinically relevant doses were available for 24 of the top 31 combinations over 24 hours [13, 15–25], whereas only 4 of these combinations had validated stability data for 48-hour administration [16, 22–25].

Mean morphine equivalent dose

Table 5 presents the mean daily doses of all prescribed opioids, converted into morphine-equivalent doses according to current national guidelines [26].

Table 5. Mean morphine equivalent daily dose for prescribed opioids.

Opioid	Mean parenteral daily dose (mg)	Mean oral morphine equivalent dose (mg)
Alfentanil hydrochloride	1.8	54
Diamorphine hydrochloride	7.5	22.5
Morphine sulphate	19.14	38.28
Oxycodone hydrochloride	21.09	84.36

N.B Current evidence suggests that doses of parenteral morphine and parenteral oxycodone are equivalent (i.e. 1:1) [27]

To our knowledge, this study represents the first UK analysis of CSCI prescribing patterns over continuous periods extending up to seven days. In this evaluation, 55% of CSCIs (n = 320) remained unchanged for two or more consecutive days, compared with 72% (n = 38) observed in a previous pilot study [14]. Notably, one-third of these unchanged infusions included weekend days, which are typically associated with reduced staffing in NHS hospitals. These findings indicate a potential patient group for whom a 48-hour CSCI infusion could be feasible, offering both reduced patient interventions and more efficient use of healthcare professional time.

Oxycodone was the most frequently prescribed opioid in this study, aligning with recent national surveys of CSCI practice [28]. This is despite national guidance recommending morphine sulphate as the first-line opioid based on cost-effectiveness [29]. Morphine remained widely used, appearing in five of the six most common drug combinations.

The two most frequently prescribed drug combinations mirrored the results of national prescribing surveys, while the third most common combination contained the “four core” medications essential for end-of-life care (morphine, midazolam, levomepromazine, and glycopyrronium) [30]. Interestingly, this combination was only used at one site (site 7), a pattern that may reflect differences in clinician experience with CSCI prescribing. This was further evidenced by frequent, incremental dose adjustments observed in patient prescriptions. The fourth most common combination (morphine + midazolam + levomepromazine) ranked sixth in prior evaluations.

Of the top 31 drug combinations, only four had laboratory-validated chemical stability and compatibility data for 48-hour administration. Given the potential increased risk of infection with extended-duration CSCIs, a careful assessment of ward-based versus pharmacy-based aseptic preparation and the potential inclusion of in-line antimicrobial filters [31] is required before clinical adoption.

Alternative approaches, such as using long-acting agents (e.g., levomepromazine) or transdermal delivery, may not be suitable in all cases. Large subcutaneous doses can increase adverse effects and injection site irritation, and the majority of drugs commonly used in palliative care via CSCI have action durations of less than 24 hours, necessitating daily visits. Moreover, adjusting doses in response to patient condition changes is more flexible with CSCIs compared to long-acting or transdermal medications, making 48-hour CSCIs advantageous for maintaining stable plasma drug levels.

Strengths and limitations

This evaluation is the first of its kind, highlighting the potential utility of extended-duration CSCIs to improve NHS resource use and patient care. Delays in obtaining local Research and Development approvals limited the volume of data collected. Additionally, the study did not capture whether patients received daily clinical review or the rationale behind unchanged doses after review. In routine practice, nursing staff continuously monitor patient symptoms and infusion devices, escalating care if needed. As this study provided a "snapshot" of prescribing practices, detailed patient demographics were not collected. Future national registries could capture such information, enabling identification of patient groups most likely to benefit from 48-hour infusions.

A further limitation is that all participating hospitals were located in the North of England, primarily in the North-West, and the study was restricted to acute hospital settings.

Conclusion

This evaluation identified a patient population whose CSCI prescriptions did not require changes to drugs or dosages for at least 48 hours. These findings suggest that extending CSCI infusion duration from 24 to 48 hours may be feasible for select patients, potentially improving efficiency and patient experience in end-of-life care.

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