Compatibility of an injectable high strength oxycodone formulation with typical diluents, syringes, tubings, infusion bags and drugs for potential co-administration

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Abstract

Study objectives: To investigate the physical and chemical compatibility of oxycodone hydrochloride injection 50 mg/mL with common infusion fluids, materials used in the components of dosing assemblies, and a range of drugs routinely used in palliative care.

Methods: Oxycodone hydrochloride injection 50 mg/mL, either undiluted or diluted to 3 mg/mL (1 in 17 mL) in 0.9% weight-in-volume sodium chloride, 5% weight-in-volume dextrose or Water For Injections was stored in a range of syringes, tubings and infusion bags for up to seven days at 4°C and 25°C. Undiluted and diluted oxycodone hydrochloride injection solutions were also mixed with parenteral formulations of a range of drugs commonly used in palliative care and stored for 24 hours at 25°C. The appearance, pH and active content of the solutions were monitored during storage.

Results: Oxycodone hydrochloride injection 50 mg/mL was physically and chemically compatible with the infusion fluid diluents and, whether undiluted or diluted, with all the syringes, tubing, and infusion bags tested, with the exception of polycarbonate syringes after 24 hours. It was also compatible with the drugs selected for potential co-administration, though certain limitations were evident in the case of cyclizine lactate.

Conclusion: Oxycodone hydrochloride injection 50 mg/mL is compatible with a range of infusion fluids, dosing assemblies, and drugs regularly used for administration by the parenteral route in palliative care.

Keywords

Dosing assemblies, drug compatibility, oxycodone hydrochloride, palliative care, parenteral infusions

Introduction

Oxycodone hydrochloride is a semi-synthetic opioid derivative with a phenanthrene structure. In the United Kingdom, it is licensed for the treatment of moderate to severe pain in patients with cancer and post-operative pain, and severe pain requiring the use of a strong opioid. Clinical studies show it to be effective for managing a number of pain conditions [1], including moderate to severe cancer pain [2-4]. Oxycodone hydrochloride exerts full opioid agonist activity similar to that of morphine and other opioid analgesics. It is currently available in several countries in Europe (including the UK) and in the US as prolonged release tablets, immediate release solutions and capsules for oral administration, and as a 10 mg/mL injection. A high strength oxycodone injection formulation (50 mg/mL) has been developed to extend the flexibility of administration of the product when used in syringe drivers by decreasing the volume required for administration of the required dose.

It is common practice in palliative care to administer parenteral forms of opioid analgesics, for example, diamorphine, in conjunction with other drugs, typically to counteract nausea and vomiting, bowel colic, respiratory secretions, and restlessness or confusion [5]. Provided that there is evidence of compatibility, the most convenient approach is for the injectable products to be mixed in syringe drivers or diluted with infusion fluids for co-administration.

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A previous study has shown that extemporaneously prepared 100 mg/mL solutions of oxycodone hydrochloride in sterile water are stable for up to 35 days when stored at 24°C in plastic syringes and, after dilution in infusion fluid, in polyvinyl chloride (PVC) bags [6].

The purpose of the studies described in this report was to provide information on the compatibility of oxycodone hydrochloride injection 50 mg/mL with common infusion fluid diluents, materials used in dosing assemblies (syringes, tubing, and infusion bags), and a range of drugs routinely considered for parenteral application in palliative care.

Methods

Compatibility with diluents and materials

The selection of test materials for the study was based on a review of diluents, syringes, tubing, and infusion bags commonly used for parenteral administration. One representative brand or supplier of each infusion fluid or assembly component made from a specific material was chosen (see Table 1).

Each syringe, tube or infusion bag was tested with oxycodone hydrochloride injection 50 mg/mL, both undiluted and diluted to 3 mg/mL in 0.9% sodium chloride, 5% dextrose and Water For Injections (WFI). Each solution was assayed in bulk and after dwelling in dosing apparatus. Samples were stored in glass vials as controls throughout the study.

For all syringe, tubing, and PVC bag studies, dilutions were made using 0.9% sodium chloride, 5% dextrose and WFI supplied in PVC bags. For ethyl vinyl acetate (EVA) bag studies, dilutions were made using 0.9% sodium chloride and 5% dextrose supplied in PVC-free (polyolefin) bags and WFI supplied in glass vials.

Immediately after preparation, each bulk solution was checked for appearance (coloration, crystallisation, particulates, etc.) and clarity using the Ph.Eur. test method [7]. The pH of all bulk solutions were measured and recorded. Each bulk solution was sampled in triplicate and analysed for active content and related substances, i.e. degradation products and synthetic impurities, using high performance liquid chromatography (HPLC). The HPLC assay method for oxycodone injection was developed and validated for detector linearity, system precision, assay accuracy, method precision and specificity. Chromatographic system suitability checks were included in the method. Full details of the HPLC assay are available on request from the author.

Duplicate assemblies containing the solutions were prepared and sampled for analysis immediately after transfer into the syringe, bag, or tubing, and then stored for up to seven days protected from light. Syringes and bags were tested in static systems at 4°C and 25°C. Tubing was tested in a dynamic system by attachment to a polypropylene syringe and installation in a syringe driver (IVAC P7000 syringe pump) at 25°C. Solutions were infused at a rate of about 0.5 mL per hour. The solutions were checked for appearance and pH and analysed for active content, related substances and spurious and/or unexpected peaks by HPLC at one and seven days (static systems) and one and three days (dynamic systems). Results were considered to demonstrate compatibility if they met the following acceptance criteria:

- appearance and clarity were the same as the bulk solution
- pH of the solutions were ≤ ±0.2 pH units of the bulk solution
- mean active content ≤ ±2% of the bulk solution
- mean oxycodone related substances content ≤ ±20% at levels ≥0.05%
- There were no interfering or spurious peaks on the HPLC analysis.

Table 1: Materials used in compatibility testing of infusion fluids and dosing assemblies

Material	Source
0.9% w/v sodium chloride in polyvinyl chloride (PVC) [Viaflex] bags	Baxter Healthcare Ltd
0.9% w/v sodium chloride in PVC-free [Freeflex] bags	Fresenius Kabi Ltd
5% w/v dextrose in PVC [Viaflex] bags	Baxter Healthcare Ltd
5% w/v dextrose in PVC-free [Freeflex] bags	Fresenius Kabi Ltd
Water For Injections (WFI) in PVC [Viaflex] bags	Baxter Healthcare Ltd
WFI in glass vials*	Hameln Pharma
Polypropylene [Plastipak] syringes (50 mL)	Becton Dickinson
Polycarbonate [Angiodyn spectraline] syringes (20 mL)	B. Braun Medical UK Ltd
PVC tubing	Vygon
Polyethylene [V-green] tubing	Vygon
Ethyl vinyl acetate infusion bags [Clintec]	Baxter Healthcare Ltd
*Infusion fluid compatibility only.	

Compatibility with drugs

Representative brands of injectable forms of a number of drugs commonly used in co-administration with opioid analgesics in palliative care [5, 8] were selected (see Table 2).

Table 2: Type and volume of drug product used in compatibility testing

Product name	Strength	Manufacturer or supplier (at time of study)	Required volume of co-administered drug product for high-dose combination (mL)	Required volume of co-administered drug product for low-dose combination (mL)
Hyoscine butylbromide (Buscopan)	20 mg/mL	Boehringer Ingelheim	3	1.5
Dexamethasone sodium phosphate	4 mg/mL	Faulding/Mayne	10	5
Haloperidol (Haldol)	5 mg/mL	Janssen-Cilag	3	1.5
Midazolam hydrochloride (Hypnovel)	10 mg/2 mL	Roche	20	10
Hyoscine hydrobromide	400 µg/mL	UCB	6	3
Metoclopramide hydrochloride (Maxolon)	10 mg/2 mL	Shire	20	10
Levomepromazine hydrochloride (Nozinan)	25 mg/mL	Link	8	4
Cyclizine lactate (Valoid)	50 mg/mL	Amdipharm	(a) 1	(b) 1.5, (c) 3
Glycopyrronium bromide (Robinul)	200 µg/mL	Anpharm	12	6
Ketamine hydrochloride (Ketalar)	100 mg/mL	Pfizer	8	4

Screening was conducted with 'high-dose' and 'low-dose' combinations of oxycodone hydrochloride injection 50 mg/mL and co-administered drugs to provide a wide compatibility profile for use in clinical practice. The high- and low-dose values for the co-administered drug were based on literature values of recommended maximum daily doses, where available [5, 8, 9], or on advice from a medical consultant. The high-dose combinations consisted of 10 mL of undiluted oxycodone hydrochloride injection 50 mg/mL plus the appropriate volume of the co-administered drug product containing the maximum recommended daily dose of the drug (see Table 2). The low-dose combinations consisted of 5 mL of oxycodone hydrochloride injection 50 mg/mL mixed with 50% of the volume containing the maximum daily doses of the co-administered drugs and then diluted to 17 mL with 0.9% sodium chloride or WFI (see Table 2).

Before the full screening was undertaken, preliminary visual screening of the high- and low-dose combinations was carried out to check for precipitation or crystallisation. Each dose combination was prepared in a glass vial and mixed thoroughly by shaking. Each sample was checked against a black background for signs of precipitation and/or crystallisation after 24 hours storage at ambient temperature (see Table 3). As a result of physical incompatibility occurring in high-dose combinations using cyclizine lactate injection 50 mg/mL, screening of oxycodone hydrochloride injection and cyclizine lactate injection was performed at several doses of cyclizine. This ensured that doses of cyclizine which were selected for the full screening showed no precipitation/crystallisation (see Table 4).

For the full screening, the high- and low-dose combinations of oxycodone hydrochloride injection 50 mg/mL and co-administered drug were mixed vigorously by shaking and the solution was checked immediately and 15 minutes after preparation for any sign of physical incompatibility, e.g. crystallisation or precipitation. If no such incompatibility was evident in the dose combinations, syringes were filled and stored at 25°C ± 2°C protected from light and additional samples stored in glass vials as controls. The syringes were sampled at 0, 6 and 24 hours and the sample solutions were checked for appearance and pH, and analysed for oxycodone and co-administered drug content. The HPLC assay methods for each of the co-administered

Table 3: Visual screening of oxycodone hydrochloride injection 50 mg/mL and co-administered drug

Drug product	Appearance*
Hyoscine butylbromide	Clear, colourless solution
Dexamethasone sodium phosphate	Clear, colourless solution
Haloperidol	Clear, colourless solution
Midazolam hydrochloride	Clear, colourless solution
Hyoscine hydrobromide	Clear, colourless solution
Metoclopramide hydrochloride	Clear, colourless solution
Levomepromazine hydrochloride	Clear, colourless solution
Cyclizine lactate	Crystallisation observed
Glycopyrronium bromide	Clear, colourless solution
Ketamine hydrochloride	Clear, colourless solution

*After 24 hour storage at ambient temperature.

Table 4: Preliminary visual screening of combinations of oxycodone hydrochloride injection 50 mg/mL and cyclizine lactate injection 50 mg/mL		
Volume ratio (mL) of oxycodone hydrochloride injection: cyclizine lactate combination	**Initial appearance**	**Appearance at 24 hours**
10 : 3	Clear, colourless solution	Crystals observed
10 : 2	Clear, colourless solution	Crystals observed
10 : 1 (equivalent to (a) in Table 2)	Clear, colourless solution	Clear, colourless solution
Volume ratio (mL) of oxycodone hydrochloride injection: cyclizine lactate injection diluted to 17 mL with Water For Injections		
5 : 1.5	Clear, colourless solution	Clear, colourless solution
5 : 3	Clear, colourless solution	Clear, colourless solution

drugs were developed and validated for detector linearity, system precision, assay accuracy, method precision and specificity. Chromatographic system suitability checks were included in the method. Full details of these HPLC methods are available on request from the author.

For all samples, the results obtained at each timepoint were compared with those from the initial analysis of the bulk solutions. Results were considered acceptable if they met the following acceptance criteria:

- appearance and clarity were the same as the bulk solution
- pH of the solutions were ≤ ±0.2 pH units of the bulk solution
- mean oxycodone hydrochloride and co-administered drug content ≤ ±2% of the bulk solution.

Results

Syringes, tubes and infusion bags

The results of the analyses are shown in Table 5 and Table 6. All preparations of oxycodone hydrochloride injection met the acceptance criteria described in the methods, at all the storage conditions tested, with the exception of polycarbonate syringes when stored beyond 24 hours.

Drugs for co-administration

The results of the preliminary visual screening are shown in Table 3 and Table 4. All solutions used for full screening appeared clear and colourless, i.e. as the original solutions, after 24 hours.

The results of the full screening are shown in Table 7. All of the combinations met the acceptance criteria described in the methods.

Discussion

Oxycodone hydrochloride injection 50 mg/mL, either undiluted or diluted to 3 mg/mL (1 in 17) with representative brands of 0.9% sodium chloride, 5% dextrose, or WFI, was found to be physically and chemically stable for up to seven days at 4°C and 25°C when in contact with representative brands of polypropylene syringes, polyethylene or PVC tubing, and PVC or EVA infusion bags. Assay of oxycodone and related substances and

Table 5: Compliance with acceptance criteria of oxycodone hydrochloride injection 50 mg/mL stored in dosing assemblies at 4°C									
Solution	**Compliance with acceptance criteria**								
		Syringes material				**Infusion bag material**			
		Polypropylene		**Polycarbonate**		**Ethyl vinyl acetate**		**Polyvinyl chloride**	
	Time (days)	**1**	**7**	**1**	**7**	**1**	**7**	**1**	**7**
Oxycodone hydrochloride injection (50 mg/mL)									
Undiluted		✓	✓	✓	x	✓	✓	✓	✓
Diluted to 3 mg/mL with									
0.9% w/v sodium chloride		✓	✓	✓	✓	✓	✓	✓	✓
5% w/v dextrose		✓	✓	✓	x	✓	✓	✓	✓
Water For Injections		✓	✓	✓	x	✓	✓	✓	✓
✓Indicates that the solution stored as indicated met the acceptance criteria and 'x' indicates that the solution stored as indicated did not meet the acceptance criteria.									

Table 6: Compliance with acceptance criteria of oxycodone hydrochloride injection 50 mg/mL stored in dosing assemblies at 25°C

Solution		Compliance with acceptance criteria											
		Syringes material				Tubing material				Infusion bag material			
		Polypropylene		Polycarbonate		Polyvinyl chloride		Polyethylene		Ethyl vinyl acetate		Polyvinyl chloride	
	Time (days)	1	7	1	7	1	3	1	3	1	7	1	7
Oxycodone hydrochloride injection (50 mg/mL)													
Undiluted		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Diluted to 3 mg/mL with													
0.9% w/v sodium chloride		✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓
5% w/v dextrose		✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓
Water For Injections		✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓

✓Indicates that the solution stored as indicated met the acceptance criteria and 'x' indicates that the solution stored as indicated did not meet the acceptance criteria.

the solution pH complied with the applied acceptance criteria for all solutions, with the exception that a significant increase in the level of related substances was seen in solutions in contact with polycarbonate syringes at seven days' storage, particularly in diluted solutions stored at 25°C. Data obtained on all solutions after one day of storage was acceptable. Storage of solutions in polycarbonate syringes beyond 24 hours is therefore not recommended. The incidence of lower oxycodone assay figures in solutions in contact with EVA bags suggests some sorption onto the internal surface of the bags. The slight increase in oxycodone assay observed in the dynamic runs was considered to be a result of evaporation from open collection vessels.

In the preliminary visual screening of compatibility with drugs for co-administration, crystal formation was seen in the high-dose combination of oxycodone hydrochloride injection 50 mg/mL and cyclizine lactate injection 50 mg/mL. In the full screening, decreasing the volume of cyclizine lactate injection 50 mg/mL from 3 mL to 1 mL, i.e. to one third of the maximum daily dose (see Table 4) sufficiently reduced the concentration of cyclizine lactate to avoid precipitation.

For combinations containing cyclizine lactate, 0.9% sodium chloride was not used as a diluent as there is an interaction between cyclizine lactate and 0.9% sodium chloride leading to precipitation [8]. This is most likely to be caused by formation of the sparingly soluble cyclizine hydrochloride salt and is noted in the literature. No precipitation was seen when WFI was used as a diluent in the full screening.

For practical administration purposes, allowing for an adequate safety margin, cyclizine lactate concentrations should not exceed 3 mg/mL when mixed with oxycodone hydrochloride injection, undiluted. The low-dose combination studies indicate that higher concentrations of cyclizine lactate injection 50 mg/mL, up to 8 mg/mL can be administered with oxycodone hydrochloride if the dose of oxycodone hydrochloride injection 50 mg/mL is reduced to 5 mL and the drug combination is sufficiently diluted with WFI (see Table 2 (b) and (c)). Cyclizine lactate will precipitate in the presence of 0.9% sodium chloride, and so any dilution of oxycodone hydrochloride injection for use with cyclizine lactate injection should be made with WFI.

It should be noted that the results reported in this paper apply to the products used in this study. It is likely that they would be applicable to assemblies and formulations containing the same materials and drugs produced by other manufacturers, but this cannot be confirmed without carrying out further studies to ensure that the compatibility profile is acceptable.

Sterility testing of undiluted oxycodone hydrochloride injection 50 mg/mL, once removed from the original ampoule, or of the diluted solutions, has not been undertaken. Reference should be made to the British National Formulary guidelines for intravenous additives for information on aseptic procedures [10].

Table 7: Compliance with the acceptance criteria relating to the content of oxycodone hydrochloride and co-administered drug in combinations of oxycodone hydrochloride injection 50 mg/mL and drug stored at 25°C

Co-administered drug	Time (hours)	Oxycodone hydrochloride content of solution			Co-administered drug content of solution		
		High-dose combination	Low-dose combination		High-dose combination	Low-dose combination	
Diluent		–	Diluted in 0.9% sodium chloride	Diluted in WFI	–	Diluted in 0.9% sodium chloride	Diluted in WFI
Hyoscine butylbromide	6	✓	✓	✓	✓	✓	✓
	24	✓	✓	✓	✓	✓	✓
Dexamethasone sodium phosphate	6	✓	✓	✓	✓	✓	✓
	24	✓	✓	✓	✓	✓	✓
Haloperidol	6	✓	✓	✓	✓	✓	✓
	24	✓	✓	✓	✓	✓	✓
Midazolam hydrochloride	6	✓	✓	✓	✓	✓	✓
	24	✓	✓	✓	✓	✓	✓
Hyoscine hydrobromide	6	✓	✓	✓	✓	✓	✓
	24	✓	✓	✓	✓	✓	✓
Metaclopramide hydrochloride	6	✓	✓	✓	✓	✓	✓
	24	✓	✓	✓	✓	✓	✓
Levomepromazine hydrochloride	6	✓	✓	✓	✓	✓	✓
	24	✓	✓	✓	✓	✓	✓
Cyclizine lactate*	6	✓	–	✓	✓	–	✓
	24	✓	–	✓	✓	–	✓
Glycopyrronium bromide	6	✓	✓	✓	✓	✓	✓
	24	✓	✓	✓	✓	✓	✓
Ketamine hydrochloride	6	✓	✓	✓	✓	✓	✓
	24	✓	✓	✓	✓	✓	✓

*1 mL cyclizine lactate used for high-dose volumes based on results from Table 4; high-dose combination: a solution containing the maximum recommended daily dose of the co-administered drug plus 10 mL of oxycodone hydrochloride injection (50 mg/mL); low-dose combination: a solution containing 50% of the volume containing the maximum daily dose of the co-administered drug plus 5 mL of oxycodone hydrochloride injection (50 mg/mL) diluted to 17 mL with saline or WFI.
WFI: Water For Injections.
✓Indicates that the solution stored as indicated met the acceptance criteria.

Conclusion

Under the conditions applied, oxycodone hydrochloride injection 50 mg/mL is compatible with a range of infusion fluids, syringes, tubes, infusion bags, and drugs which are regularly used for administration by the parenteral route to treat conditions commonly arising during palliative care of patients.

The use of polycarbonate syringes beyond 24 hours must be avoided.

Caution must be taken in the selection of high concentration ratios of oxycodone hydrochloride injection 50 mg/mL and cyclizine lactate injection 50 mg/mL and the combination should be sufficiently diluted to ensure physical compatibility. WFI should be used as a diluent when oxycodone hydrochloride injection 50 mg/mL and cyclizine lactate injection 50 mg/mL are to be co-administered by the intravenous or subcutaneous routes. Dilution of cyclizine lactate with 0.9% sodium chloride, alone or in combination with oxycodone hydrochloride injection, must be avoided.

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