Original Article

Effect of Tubing on Loss of Clonazepam Administered by Continuous Subcutaneous Infusion

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Abstract
Previous studies have reported loss of clonazepam from solutions administered intravenously from plastic infusion bags and administration sets. In palliative care, clonazepam is sometimes administered through syringe drivers using polyvinyl chloride (PVC) infusion tubing. No data currently exist to show whether use of PVC tubing affects the amount of clonazepam actually received by the patient. This study compared the use of two different types of PVC tubing with a non-PVC tubing. Solutions containing clonazepam or clonazepam and morphine were prepared with either normal saline or water for injection as diluent. Concentrations of morphine and clonazepam were determined using high-performance liquid chromatography. Significant loss of clonazepam (up to 50%) was observed in all solutions infused through PVC tubing. Solutions infused through non-PVC tubing retained greater than 90% of the initial concentration of clonazepam. It is recommended that when administering clonazepam using a syringe driver, non-PVC tubing be used. J Pain Symptom Manage 2006;31:563–567. © *2006 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Subcutaneous drug administration, clonazepam, morphine sulfate, palliative care, stability, sorption

Introduction

Clonazepam, a benzodiazepine, is used in palliative care for its anxiolytic effect, anticonvulsant activity, and analgesic effects in neuropathic pain.[1] It can be given orally or administered as a subcutaneous bolus or as a 24-hour continuous subcutaneous infusion using a syringe driver or a similar device. When preparing clonazepam for infusion, diluents such as sodium chloride 0.9% or water for injection are added. On occasion, other medications, such as morphine, may also be present in the infusion solution. These solutions, prepared in polypropylene syringes, are slowly administered over 24 hours through

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infusion tubing. Different types of infusion tubing are used, some of which are made of polyvinyl chloride (PVC).

Sorption (loss) of benzodiazepines to PVC bags and tubing has been reported in intravenous (IV) solutions of clonazepam administered over a few hours.[2,3] Loss of clonazepam into IV tubing has been reported to be concentration and flow dependent, with use of polyethylene-coated tubing resulting in no loss of clonazepam.[3] Concentrations, volumes, and flow rates used in the studies cited above differ considerably from those commonly used in palliative care. Data on the effect of tubing or presence of another drug on clonazepam administered using a syringe driver have not been reported in the literature.

The aim of this study was to investigate whether significant loss of clonazepam occurred when clonazepam was delivered through different types of tubing over 24 hours using a syringe driver. The effect of diluent, drug concentration, and presence of morphine was also investigated.

Methods

Reagents

The reagents used were ampules of clonazepam (1 mg/mL); pure clonazepam powder (Roche Products Pty. Ltd., Dee Why, New South Wales, Australia); ampules of morphine sulfate and pure morphine sulfate powder (David Bull Laboratories Pty. Ltd., Mulgrave, Victoria, Australia); nalorphine hydrobromide B.P. (Wellcome Foundation Ltd., London, UK); sodium chloride injection 0.9% and water for injection (Pharmacia West Ryde, Australia); disodium hydrogen orthophosphate and sodium dihydrogen orthophosphate (AR, Sigma Chemical Co., St. Louis, MO, USA); and acetonitrile and methanol (ChromAR HPLC, Mallinckrodt, Clayton South Australia Pty. Ltd.). Water used in preparation of solutions was purified using a Millipore reverse osmosis and filtration system (North Ryde, NSW, Australia).

Experimental Design

Eight different solutions containing clonazepam either alone or in combination with morphine were prepared as outlined in Table 1. For each solution, 10 replicates were prepared

Table 1
Syringe Combinations Prepared and Percentage of Initial Morphine Concentration and Initial Clonazepam Concentration Observed in Solutions at 24 Hours

Syringe Combination			Morphine (% of initial concentration)					Clonazepam (% of initial concentration)				
Diluent	Morphine (mg)	Clon (mg)	GB	SYR	NONPVC (IVAC)	PVC1 (TUTA)	PVC2 (BRAUN)	GB	SYR	NONPVC (IVAC)	PVC1 (TUTA)	PVC2 (BRAUN)
NS	30	2	99.7 (2.0)	96.2 (1.4)	98.4 (1.0)	98.4 (0.9)	98.5 (1.8)	96.0 (1.9)	93.8 (1.7)	92.3 (1.0)	59.2[a] (0.6)	49.1[a] (3.0)
NS	90	4	100.9 (1.9)	100.5 (1.0)	102.4 (1.0)	103.3 (1.9)	102.4 (1.9)	96.7 (2.2)	96.7 (2.2)	97.9 (7.7)	74.1[a] (3.1)	68.2[a] (2.1)
NS	–	2	–	–	–	--	–	97.2 (1.3)	94.4 (1.6)	93.1 (3.4)	65.2[a] (1.9)	47.7[a] (1.3)
NS	–	4	–	–	–	--	–	95.7 (0.7)	95.3 (1.8)	93.0 (1.3)	74.2[a] (0.4)	61.2[a] (0.2)
WFI	30	2	100.4 (2.2)	98.6 (0.7)	100.2 (1.4)	97.2 (1.8)	99.9 (1.0)	99.5 (2.5)	95.9 (1.9)	93.3 (3.5)	64.8[a] (1.0)	52.2[a] (1.2)
WFI	90	4	98.6 (2.8)	98.1 (1.6)	99.6 (2.9)	98.1 (1.5)	100.0 (1.6)	96.7 (2.2)	96.6 (2.3)	96.7 (2.2)	80.0[a] (2.0)	68.6[a] (3.1)
WFI	–	2	–	–	–	--	–	93.9 (1.7)	90.3 (1.4)	91.9 (1.7)	58.4[a] (1.5)	47.0[a] (2.2)
WFI	–	4	–	–	–	--	–	96.1 (1.8)	94.4 (0.6)	92.0 (3.7)	72.3[a] (1.3)	63.4[a] (2.3)

NS = 0.9% sodium chloride solution; WFI = water for injection; Clon = Clonazepam; GB = glass bottle; SYR = syringe; () = SD.
[a] = significant difference ($p < 0.05$) when compared to syringe concentration using Tukey Multiple Range Test.

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