CLINICAL INVESTIGATION

Plasma Concentrations Following Application of Whole versus Cut Transdermal Clonidine Patches To Critically Ill Children

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Clonidine is used for hypertension and narcotic withdrawal prophylaxis in adults and children. This study described plasma absorption of clonidine from whole and cut transdermal clonidine patches. This was a retrospective descriptive study in an 18 bed multidisciplinary pediatric intensive care unit, evaluating 15 critically ill children with a median age of 1.1 years (range 0.3–11 years) treated with transdermal clonidine for narcotic withdrawal prophylaxis, and who had plasma clonidine concentrations measured. An assessment of the relationship between clonidine dose and patch integrity (whole vs. cut) with plasma concentrations was performed, with further analysis by Spearman Correlation Coefficient. Clonidine doses averaged 7.5±4.2 μg/kg/day (range 2.3–20 μg/kg/day) for 9.8±4.3 days (range 4–20 days). There were 9 cut patches and 6 whole patches. The average prescribed dose delivered by cut patches was 6.4±3 μg/kg/day, resulting in a mean plasma concentration of 1±1.1 ng/mL (range <0.05–3.3 ng/mL). The average prescribed dose delivered by whole patches was 7±1.7 μg/kg/day, resulting in a mean plasma concentration of 0.55±0.3 ng/mL (range 0.13–1.5 ng/mL). The Spearman Correlation Coefficient was calculated to evaluate the correlation between dose and concentration. For whole and cut patches the correlation coefficient was 0.94 (P=0.005) and 0.72 (P=0.002), respectively. Doses ranging from 1.7 to 20 μg/kg/day using whole patches resulted in no plasma concentrations >2 ng/mL. However, a plasma concentration >2 ng/mL was achieved with a dose of 8.8 μg/kg/day delivered by a cut patch. In addition, the 2 samples that resulted in undetectable concentrations were taken from patients who were treated with cut patches. The results from this pilot study suggest that critically ill children absorb clonidine from transdermal patches, but the rate and extent of absorption appears to be more predictable with the use of whole patches compared to patches that have been cut.

KEYWORDS: clonidine, patch, transdermal

J Pediatr Pharmacol Ther 2004;9:43-8

INTRODUCTION

Children who require mechanical ventilation commonly receive prolonged intravenous analgesia and sedation. The use of opiates and sedatives for more than five days often results in narcotic and benzodiazepine tolerance and dependence.[1-4] The management of withdrawal symptoms is a challenge frequently faced in the pediatric intensive care unit (PICU) setting. Few guidelines exist to treat or prevent withdrawal symptoms in pediatric patients.[5-7] A medication with minimal side effects that provides adequate prophylaxis against withdrawal is desirable in this setting.

Clonidine, widely used as an antihypertensive medication, is an alpha-2 adrenergic receptor agonist that centrally inhibits presynaptic sympathetic nervous system outflow. Clonidine's mechanism of action results in a decrease in cir-

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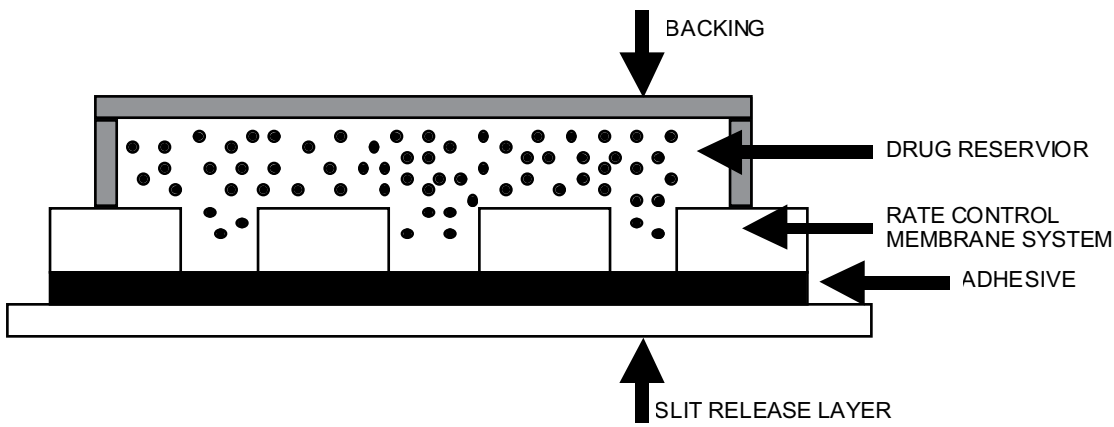
culating blood levels of epinephrine and norepinephrine. This action can prevent the symptoms of excessive catecholamine release, which occurs during opiate withdrawal.[8,9] Clonidine reduces opiate withdrawal symptoms when used in adults[8,10-13] but data is limited in critically ill children.[2,14]

Oral clonidine may reduce narcotic abstinence symptoms in neonates exposed to methadone *in utero*.[15] The utility of clonidine as a treatment for opiate withdrawal was first documented in 1978.[10] Several studies have been published since then describing its use in the management of narcotic withdrawal. These studies document oral clonidine doses of 5 μg/kg/day, and other regimens that start with 100 μg/day orally with dose increases titrated to achieve the desired clinical effect.[11,13,16-18] The use of clonidine for treatment of neonatal narcotic abstinence syndrome was well documented in 1984 using doses of 0.5 to 4 μg/kg/day.[19] A single case series suggests the utility of transdermal clonidine in the prevention of opioid withdrawal symptoms following laryngotracheal reconstruction in PICU patients.[14] However, clonidine plasma concentrations and pharmacokinetics were not assessed in this case series. Although a literature search did not reveal any studies correlating plasma concentrations with efficacy in the treatment of narcotic withdrawal, plasma concentrations >2 ng/mL resulted in an increased occurrence of side effects[20] including dry mouth, bradycardia and sedation.[13,16,17] There currently is no established reference range for plasma clonidine concentrations in the treatment of pediatric narcotic withdrawal.

Clonidine is available for use in tablet form, epidural and IV use, rectal use, and as a transdermal patch. Oral delivery is not practical for all critically ill children. Epidural administration is invasive and requires extensive monitoring. The transdermal approach is a rational route of drug administration in the PICU setting. Transdermal clonidine (Catapres-TTS, Transdermal Therapeutic System - Boehringer Ingelheim, Ridgefield CT) is a multi-layered unit that releases drug at a constant rate when applied to intact skin (Figure 1). The system includes a 4-layer laminate consisting of an occlusive protective backing that maintains proper skin hydration for drug delivery, a gelled reservoir of active drug dispersed within a highly drug-permeable matrix, a microporous membrane that controls the constant dosage rate, and an adhesive coating that attaches and primes the skin surface with drug. Prior to use, a protective slit release liner of polyester that covers the adhesive layer is removed. Following application to intact skin, the clonidine contained in the adhesive layer saturates the skin site below. Clonidine in the drug reservoir then begins to flow through the rate-controlling membrane and adhesive layer into the systemic circulation via the capillaries within the skin.[21] The amount of drug delivered is proportionate to the surface area of the patch. The 3.5, 7 and 10.5 cm^2 systems deliver 100, 200 and 300 μg/day, respectively.[22] In adults, steady state is attained within two to three days after whole patch application, and consistent clonidine concentrations are maintained without the peaks and troughs associated with conventional oral therapy.[20] In clinical practice, especially when caring for pediatric patients, doses less than 100 μg/day may be desired. If a

Figure 1. Cross sectional representation of the clonidine transdermal drug delivery system.[28]



physician prescribed a dose of 50 μg/day, half of a 3.5 cm^2 patch would be applied to the patient. At our institution, it is standard for the patches to be cut in the pharmacy. Theoretically, cutting clonidine patches in half or quarters could provide accurate dosing, but it is speculated that cutting the patch may alter the drug release properties of the dosage form. Unfortunately, there is little published data regarding the effect of cutting clonidine transdermal patches on the reliability of absorption.[23] The purpose of this pilot study was to describe the impact physically cutting clonidine transdermal patches has on systemic absorption by pediatric patients.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, the charts of 15 critically ill children treated with transdermal clonidine for narcotic withdrawal and who had a plasma clonidine concentration measured within four days of patch placement were available for review. All plasma concentrations were drawn after the placement of the first patch. Collected data included patient age, diagnosis, dose and duration of narcotic infusion, dose and duration of transdermal clonidine, patch integrity (cut or whole), and the time after patch placement when the blood was collected for plasma concentration measurement. During the time period reviewed, there were no predetermined criteria mandating the assessment of plasma clonidine concentration in these patients. However, it was common practice at this institution for clinicians to measure plasma clonidine concentrations to assess absorption or potential association with non-specific symptoms of withdrawal or toxicity.

Plasma samples were sent to SmithKline Beecham Clinical Laboratories (Willow Grove, PA) and analyzed by high performance liquid chromatography/tandem mass spectrometry. The interday and intraday coefficient of variation for the clonidine assay were 10% and the lower limit of detection was 0.05 ng/mL.

RESULTS

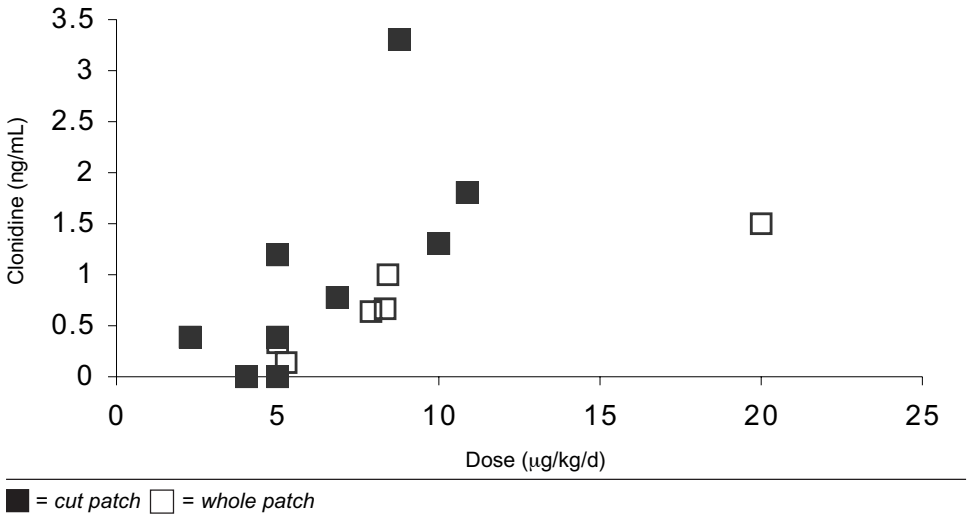
The medical records of fifteen critically ill children with a median age of 1.1 years (range 0.3–11 years) who received prolonged (>3 days) continuous morphine or fentanyl infusions and

Table: Results

Pt	Age (years)	Wt (kg)	Diganosis	Patch Integrity	Dose (mcg/kg/d)	Duration (d)	Concentration	
							Day Collected	Value
1	0.3	4.7	bronchiolitis	Cut	5	6	4	ND*
2	0.6	6.6	BPD, tracheomalacia	Cut	5	20	3	1.2
3	0.6	10.8	subglottic stenosis	Cut	4	7	4	ND
4	1.1	22	status post cricoid split pneumonia; septic shock; ARDS	Whole	20	10	3	1.5
5	4	11.8	pneumonia; toxic shock syndrome	Cut	2.3	13	3	0.4
6	2	5.7	subglottic stenosis; status post tracheal reconstruction	Whole	8.4	7	4	1
7	0.3	2.3	bronchiolitis	Cut	8.8	14	3	3.3
8	0.3	12	subglottic stenosis	Cut	10.9	7	4	1.8
9	2	10	status post cricoid split craniopharyngioma resection	Whole	8.3	7	3	0.68
10	1.4	12.6	nephrectomy; pancreatic resection	Cut	5	7	3	0.38
11	1.3	38	epilepsy requiring intubation	Whole	7.9	7	4	0.64
12	11	3	subdural abscess; sepsis syndrome	Whole	5.3	13	4	0.13
13	0.6	7.4	BPD; tracheomalacia	Cut	10	4	3	1.3
14	0.6	20	BPD, ARDS	Cut	6.8	14	4	0.79
15	6	4.7	epilpesy status post trauma	Whole	5	11	3	0.32

ARDS, acute respitatory syndrome; BPD, bronchopulmonary dysplasia; ND, not detected

Figure 2. Plasma concentration as a function of dose administered for cut (n=9) and whole (n=6) patches. Each data point represents a different patient.



subsequent treatment with transdermal clonidine were reviewed.

Results are reported in the Table. Clonidine doses averaged 7.5±4.2 μg/kg/day (range 2.3–20 μg/kg/day) for 9.8±4.3 days (range 4–20 days) for all patients. There were 9 cut patches and 6 whole patches. Clonidine plasma concentrations were drawn 3 days after patch placement for 8 patients (5 cut and 3 whole) and 4 days after patch placement for 7 patients (4 cut and 3 whole). Since plasma steady-state concentrations are achieved within two to three days after patch application, it was assumed that all measured plasma concentrations were at steady-state.

The plasma concentrations achieved as a function of dose are depicted in Figure 2. The average prescribed dose using cut patches was 6.4±3 μg/kg/day resulting in a mean plasma concentration of 1±1.1 ng/mL (range <0.05–3.3 ng/mL). The average prescribed dose using whole patches was 7±1.7 μg/kg/day resulting in a mean plasma concentration of 0.55±0.3 ng/mL (range 0.13–1.5 ng/mL). The Spearman Correlation Coefficient was calculated to evaluate the correlation between dose and concentration. For whole and cut patches the correlation coefficient (r) was 0.94 (P=0.005) and 0.72 (P=0.002), respectively. Doses ranging from 1.7 to 20 μg/kg/day using whole patches resulted in no plasma concentrations >2 ng/mL. However, a plasma concentration >2 ng/mL was achieved with a dose of 8.8 μg/kg/day delivered by a cut patch. Both samples that resulted in undetectable concentrations were taken from patients who were treated with cut patches (Table 1).

DISCUSSION

The results from this pilot study suggest that plasma clonidine concentrations resulting from placement of a cut patch are more variable than those from a whole patch. The impact of cutting transdermal patches on drug delivery is not well documented. One case report describes the use of a cut fentanyl patch in a 22-year-old male suffering from neuropathic pain in his right leg. One-fourth of a fentanyl patch (50 mcg/hour) was applied. Sixty minutes after applying one-fourth of a fentanyl patch (50 mcg/hour) the patient developed signs of opioid intoxication The patient recovered after the patch was removed.[24]

There currently is no established reference range for plasma clonidine concentrations in the treatment of pediatric hypertension or narcotic withdrawal. In adults, the antihypertensive effects correlate with plasma concentrations between 0.2 and 2 ng/mL and are dose-dependent.[20] The pharmacokinetics of clonidine have been described in adults and children. In adults, the peak plasma concentration was 1 ng/mL approximately 2 hours after an oral 300 μg dose. The elimination half-life was 8 to 14 hours.[20] Following a single intravenous dose in children, the half-life was 5.5 hours and volume of distribu-

tion was 0.96 L/kg.[25] Rectal administration of 2.5 μg/kg in children achieved an average maximal concentration of 0.77 ng/mL in approximately 52 minutes, with a terminal half-life of 12.5 hours.[26]

The pharmacokinetics of transdermal clonidine have been described in adults but not in critically ill infants and children. In adults, the intact transdermal system results in plasma clonidine concentrations comparable to those achieved with oral administration, without large fluctuations in plasma concentrations.[20] After the application of increasing sizes of transdermal clonidine systems (0.1, 0.2, and 0.3 mg) to the upper outer arm of six adult subjects, the mean steady-state plasma concentrations were 0.39, 0.84, and 1.12 ng/mL, respectively. Plasma concentrations within the reference range were achieved by two to three days after patch placement. The half-life ranged from 14 to 16 hours. No significant decline in plasma concentrations was noted until the tenth day of wear. In addition, there were no significant increases or decreases of plasma concentrations following patch change.[27]

This study was limited by a retrospective design that included a small sample of patients, lack of standardization of anatomic location of patch placement, lack of predetermined criteria for obtaining a plasma clonidine concentration, and a lack of consistent timing of samples after patch placement. This study included patients with a wide age range, introducing variability in terms of age-related clearance of clonidine. In addition, since the study was performed retrospectively, cutting of the patches was not standardized. There are no institutional guidelines that direct dosing, cutting or placement of the patch. Drug interactions and organ system failures that may have impacted on plasma concentrations in these critically ill patients cannot be excluded. Since data on withdrawal symptoms was inconsistently available, the therapeutic range for narcotic withdrawal treatment cannot be estimated. Serial pharmacokinetic sampling on individual patients is necessary to better describe the relationship between plasma concentration and the ability to manage narcotic withdrawal, and should include the measurement of catecholamine concentrations.

CONCLUSION

Critically ill children absorb clonidine from transdermal patches, but the rate and extent of absorption appears to be more predictable with the use of whole patches compared to patches that have been cut. A larger, prospective study is warranted to determine the pharmacokinetic profile, safety and efficacy of transdermal clonidine for the management of narcotic withdrawal prophylaxis in critically ill children.

ACKNOWLEDGMENTS We would like to thank Dr. Mark Helfaer for his editorial support and the nursing staff in the pediatric intensive care unit at A.I. Dupont Hospital for Children for their patience, cooperation and excellent care.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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