JPPT | Single Center Retrospective Study

Identification of a Conversion Factor for Dexmedetomidine to Clonidine Transitions

Jasmine Stroeder, PharmD; and Deonne Dersch-Mills, BScPharm, PharmD

OBJECTIVE To determine a conversion factor for use when switching from dexmedetomidine infusion to enteral clonidine in critically ill neonates.

METHODS This was an observational, retrospective review of conversions from dexmedetomidine to clonidine, performed in a neonatal intensive care unit (NICU) between January 2020 and December 2021. Both initial conversion factors and those resulting after a 48-hour titration period were examined. Sedation and withdrawal scores were measured, and doses were titrated based on a standardized practice within the unit.

RESULTS A total of 43 dexmedetomidine to clonidine conversions were included. The median (IQR) dexmedetomidine dose prior to conversion was 17.4 (11.3–24.0) mcg/kg/day (0.7 mcg/kg/hr) and the median (IQR) enteral clonidine dose post titration was 7.8 (4.7–9.3) mcg/kg/day (2 mcg/kg every 6 hours). This equated to a post-titration conversion factor of approximately 0.42. All neonates had also received opioid infusions while on dexmedetomidine and 60% were on concurrent opioids at the time of the clonidine conversion.

CONCLUSIONS Neonatal clinicians may find the conversion factor identified in this study a useful starting point when converting from dexmedetomidine infusion to enteral clonidine in practice and should be reminded of the most important steps in conversions (monitoring and follow-up) owing to the variability in this patient group. More studies are needed to elucidate the impact of patient-specific factors on this conversion process.

ABBREVIATIONS ACH, Alberta Children's Hospital; IV, intravenous; NICU, neonatal intensive care unit; NAS, neonatal abstinence score; N-PASS, neonatal pain, agitation, and sedation scale; WAT-1, Withdrawal Assessment Tool

KEYWORDS adrenergic alpha-2 agonists; clonidine; dexmedetomidine; neonatal intensive care; neonate

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Introduction

Neonates, particularly those who undergo surgery, commonly need analgesics and sedatives during their time in neonatal intensive care units (NICUs). Dexmedetomidine has emerged as a commonly used sedative in NICUs, and when transition to enteral feeds or removal of intravenous (IV) catheters requires a change to enteral route, clonidine is the typical replacement.[1–5]

There are limited studies evaluating the conversion from IV to enteral centrally active alpha-2 agonists; and none to date have examined this conversion specifically in neonates. The purpose of this study was to examine initial and post-titration conversion ratios for dexmedetomidine to clonidine in neonates in order to establish a neonatal-specific conversion factor that can be used by clinicians.

Materials and Methods

Study Design. This was a retrospective observational chart review examining the conversion factors used initially and those resulting after a 48-hour titration period when converting from dexmedetomidine infusion to enteral clonidine in patients admitted to the NICU at Alberta Children's Hospital (ACH) from January 2020 to December 2021. ACH NICU is a 14-bed, Level 3, outborn NICU that acts as a referral unit for neonates within southern Alberta and southeastern British Columbia who require surgical, neurocritical, or complex medical care. There are approximately 300 admissions per year, about 60% of which are surgical.

Inclusion and Exclusion Criteria. All patients admitted to the NICU at ACH from January 2020 through December 2021 who had at least 1 order for both IV dexmedetomidine and enteral clonidine were

screened for inclusion. Conversions were defined as any switch from dexmedetomidine infusion to regularly scheduled enteral clonidine, with no longer than 6 hours between.

Exclusion criteria included patients who died within 72 hours of the conversion (as the dose may have represented a palliative approach), or conversions to as-needed doses only. If clonidine was stopped within 48 hours, the conversion was excluded.

The unit has established protocols for weaning opioids and centrally active alpha-2 agonists (Supplemental Figures S1 and S2). The protocols were developed specifically for use in babies with acute post-surgical pain but are shared here to demonstrate the typical processes in our unit because the general approach is also applied to babies who do not undergo surgery. Two things about these protocols are significant regarding dexmedetomidine to clonidine conversions. Firstly, opioids are almost exclusively weaned off first, followed by alpha-2 agonists; however, *conversions* from dexmedetomidine to clonidine can occur while a patient is receiving opioids and may even occur simultaneously with conversions from IV to enteral opioids. Secondly, the frequent monitoring standards (every 4 hours) outlined in the weaning protocols are also followed during conversions, and as-needed doses of the converted medication (in this case, clonidine) are used in addition to regular dosing to maintain neonatal pain, agitation, and sedation scale (N-PASS) pain scores <3 and neonatal abstinence score (NAS) withdrawal scores <8 during the process.[6–8]

Data collected included patient gestational age at birth, postnatal age at time of medication use, all dexmedetomidine or clonidine order details, and clinical notes regarding conversions, all of which were obtained from the electronic health record (AllScripts Sunrise Enterprise version 18.4, Altera Digital Health). The initial dose of clonidine ordered was collected to determine the initial conversion factor. The dose received between 48 and 72 hours after dexmedetomidine discontinuation was collected to determine the post-titration conversion factor. This is based on typical unit practice where there is an overlap period between dexmedetomidine infusion and enteral clonidine administration of up to 24 hours, then any dose titration needed, based on sedation or withdrawal scores, is typically done in the next 24 to 48 hours. Because conversions are multifactorial and rely on many patient-specific factors, titration may result in a more appropriate converted dose.

Outcomes. The primary outcome was the relative conversion factor that emerged after the titration period. The secondary outcome was the conversion factor used initially when the clinical team made the conversion.

Analysis. Data analysis included descriptive statistics and was completed with Microsoft Excel. Medians and IQRs were reported from the presence of outliers and relatively small sample size.

Results

The above criteria identified 57 patients and 59 potential conversions (medication pairs). Exclusions were made on the basis of conversion to as-needed use only (n = 1), concurrent use (not a conversion) (n = 2), death within 72 hours of conversion (n = 5), conversions occurring outside of the NICU (n = 2), conversion from clonidine to dexmedetomidine (n = 1), and more than 6 hours passing between the medications (n = 5). After applying these exclusion criteria to each potential conversion, 43 conversions in 43 unique patients remained. It is worth noting that all included patients received both an opioid and dexmedetomidine/clonidine during their admission and 26/43 conversions were done while the patient was concurrently receiving opioids. The cohort had a median corrected gestational age of 40 weeks at the time of the conversion; however, there was a wide range of postnatal ages (6–135 days) (Table 1).

The median (IQR) dose of dexmedetomidine infusion prior to conversion was 17.4 (11.3–24.0) mcg/kg/day, or 0.7 (0.5–1.0) mcg/kg/hr (Table 2). Conversion from dexmedetomidine to clonidine occurred after a median of 18 days of dexmedetomidine infusion. The initial post-conversion dose of enteral clonidine was 7.5 (4.0–8.5) mcg/kg/day and after the 48-hour titration period it was 7.8 (4.7–9.3) mcg/kg/day, or approximately 2 mcg/kg/dose given every 6 hours. Overall, a median (IQR) post-titration conversion factor from dexmedetomidine to enteral clonidine of 0.42 (0.30–0.62) emerged.

Discussion

This study reports an approximate conversion factor clinicians can use when converting a patient from a dexmedetomidine infusion to enteral clonidine. By multiplying a patient's total daily dose of dexmedetomidine (in mcg/kg/day) by 0.4, an approximate individualized starting dose of clonidine (in mcg/kg/day) can be obtained. From here, clinicians should consider other factors such as duration of use, concomitant agents, ongoing sources of agitation, and overall plan of care to determine a final dose. Plans for inadequate or excessive dosing need to be left in place and enacted by using close monitoring and titration.

To our knowledge, there is no recommended conversion factor for dexmedetomidine to oral clonidine specific to neonates elsewhere in the literature; however, other literature in pediatric patients have provided suggested starting doses of clonidine for patients transitioning off dexmedetomidine.[2–5] Studies by both Crabtree et al[5] and Liu et al[3] report on reasonably successful transition protocols using clonidine doses of 15 to 16 mcg/kg/day in pediatric patients (median [IQR] age, 7.1 [4.7–12.2] and 3.5 [2–28.5] months) who had received median peak dexmedetomidine doses of

Table 1. Cohort Descriptors

	Median (IQR)	Range	Categories, n (%)	
GA at birth, wk N = 43 neonates	34.7 (26.2–38.0)	23.7–39.6	<28	13 (30)
			28 to <32	3 (7)
			32 to <37	10 (23)
			≥37	17 (40)
CGA at start of conversion, wk N = 43 conversions	40.2 (37.5–42.1)	29.9–49.7	<28	0 (0)
			28 to <32	2 (4)
			32 to <37	8 (18)
			37 to <44	30 (68)
			≥44	4 (10)
PNA at start of conversion, days N= 43 conversions	34 (19–72)	6–135	0–7	1 (2)
			8–14	8 (18)
			15–28	12 (27)
			29–90	17 (39)
			>90	6 (14)

CGA, corrected gestational age; GA, gestational age; PNA, postnatal age

1 and 1.6 mcg/kg/hr, respectively. To compare, our median starting clonidine dose was 7.5 mcg/kg/day and our peak dexmedetomidine dose at the time of conversion was 0.73 mcg/kg/hr. Neither of these pediatric studies reported on the dexmedetomidine doses that patients had received immediately prior to transition, however, and so a true "conversion factor" cannot be elicited or compared with our results.

To contrast our results, another study by Lee et al[2] on the use of clonidine to support dexmedetomidine withdrawal in critically ill pediatric patients (median [IQR] age, 4.3 [2–11.5] years) demonstrated that every 1-mcg/kg/hr increase in dexmedetomidine dose in the 24 hours prior to initiating clonidine was associated with a clonidine dose of 3.5 mcg/kg/day; this would transform to an equivalent conversion factor of about 0.15, which is quite a bit lower than our results suggest. It is possible that practice differences between NICUs and pediatric intensive care units account for this difference, including different scoring tools, sedation targets, and use of nondrug comfort measures. It is interesting, however, that this study's median (IQR) starting dose of clonidine was very similar to ours, 7.8 (5–12) versus 7.5 (4.0–8.4) mcg/kg/day.[2] Lastly, one institution has developed an unpublished guideline that provides a chart of suggested enteral clonidine doses corresponding to dose ranges of dexmedetomidine infusion rates; equivalent conversion factors would be in the range of 0.4 to 0.6.[9] This is reassuring because it aligns with our initial and post-titration results.

Table 2. Conversion Results*

Variable	Median (IQR)
Duration of dexmedetomidine, days	18 (11–38)
Dose of dexmedetomidine prior to conversion, mcg/kg/day	17.4 (11.3–24.0)
Initial dose of clonidine, mcg/kg/day	7.5 (4.0–8.5)
Initial conversion factor	0.37 (0.26–0.58)
Post-titration dose of clonidine, mcg/kg/day	7.8 (4.7–9.3)
Post-titration conversion factor	0.42 (0.30–0.62)

* Dexmedetomidine Dose x Conversion Factor = Clonidine Dose, in the same units.

Some limitations exist to our results. Firstly, conversion between medications and routes is always multifactorial and our study could not capture all the potential confounding factors involved. All patients in this study would have recently been receiving opioids and 60% were receiving concurrent opioids at the time of their dexmedetomidine-clonidine conversion. While this is highly representative of how dexmedetomidine and clonidine are used in clinical practice,[2–4] it is relevant in that background sedation from concurrent opioids may increase the tolerability of the conversion. Likewise, the other 40% may have been in the process of weaning or

tapering off dexmedetomidine at the time of conversion and so the converted dose of clonidine may have been purposefully decreased slightly to accommodate this. For these reasons, it is possible that our conversion factor may result in doses slightly lower than true "equivalent" doses; however, alignment with other literature in pediatrics suggests this difference is not large.[2,9] Secondly, we did not report on N-PASS or NAS scoring following the conversion; however, given our unit's practice of titrating doses to target N-PASS or NAS scores post conversion (similar to what is done in the weaning protocol shared in Supplemental Figure S2), it is likely that elevated scores would be accommodated for with increased dosages captured in the 48- to 72-hour post-titration dose and conversion factor. Finnegan NAS scoring was not designed for use in iatrogenic dependence, alpha-2-agonist withdrawal, or conversion scenarios so its use as part of the titration process may be questioned. Use of the Withdrawal Assessment Tool (WAT-1) may have been more appropriate because it has been validated for use in iatrogenic withdrawal scenarios; however, familiarity with this tool in our NICU is minimal and so NAS is preferred based solely on familiarity.[10] Lastly, our sample size is relatively small; it is however, likely large enough to provide a starting point for these conversions provided adequate follow-up monitoring occurs.

Conclusion

This study provides some of the first data on conversion from dexmedetomidine infusions to enteral clonidine specific to neonates. While conversion factors provide clinicians with an initial guide to switching between medications, high variability, particularly in neonates, dictates that the conversion calculations are one small part of the conversion process. Because there is no validated scoring tool for dexmedetomidine withdrawal, clinicians may choose to use familiar withdrawal assessment tools in addition to vital sign monitoring. Further study is needed to determine the impact of patient-specific factors (e.g., duration of dexmedetomidine use, ongoing sources of pain or agitation, use of concurrent agents such as opioids or benzodiazepines, and availability of nondrug measures) on the conversion from dexmedetomidine to enteral clonidine.

Article Information

Affiliations. Pharmacy Services, Alberta Health Services, Calgary, Alberta, Canada.

Correspondence. Deonne Dersch-Mills, BScPharm, PharmD; Deonne.dersch-mills@ahs.ca

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