JPPT | Extemporaneous Formulation

Stability of Oxandrolone in Medium-Chain Triglyceride Oil and Pharmacokinetics Following Buccal Administration of the Extemporaneous Formulation in Neonates and Adults

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OBJECTIVES Growth failure following surgical palliation of complex congenital heart defects (CHDs) is a prognosticator of poor outcomes. Many strategies for improving weight gain have been implemented in this population, with limited success. We recently described the potential of the anabolic steroid oxandrolone to improve weight gain following surgical repair of CHD when administered via a medium-chain triglyceride (MCT) oil suspension to the buccal mucosa. The current study evaluates the stability of oxandrolone in the MCT oil formulation, as well as the pharmacokinetics of oxandrolone when administered via buccal mucosa in both neonates and adults.

METHODS Stability was assessed by long-term storage of the preparation 1) at ambient conditions and 2) under photodegradative conditions for 3 days. Neonatal pharmacokinetic parameters were determined in a cohort of neonates following surgical CHD repair, whereas adult pharmacokinetics parameters were collected as part of a prospective study to evaluate the relative bioavailability of the oxandrolone in MCT oil formulation.

RESULTS We found that oxandrolone was stable in the MCT oil formulation for at least 1 month, although exposure to light hastened drug degradation. Both neonatal and adult oxandrolone pharmacokinetics were variable; however, oxandrolone in MCT oil was relatively well absorbed through the buccal mucosa (mean bioavailability = 62.5%).

CONCLUSIONS These data suggest that the variability in oxandrolone exposures is inherent to the drug, and not the formulation or route of administration. Combined, these data support further study of this novel oxandrolone in MCT oil formulation and its impact on growth following complex surgical repair of CHD in neonates.

ABBREVIATIONS AUC, area under the concentration time curve; CHD, congenital heart defect; MCT, medium-chain triglyceride

KEYWORDS adults; bioavailability; buccal administration; extemporaneous formulation; MCT oil; neonates; oxandrolone; pharmacokinetics

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Introduction

Neonates have a higher basal metabolic requirement with lower fat and protein stores than children and even older infants, resulting in limited metabolic reserve.[1] The metabolic reserve of neonates with congenital heart defects (CHD) is further taxed by inefficient cardiac function and suboptimal hemodynamics in the unrepaired state. Complex surgical intervention imposes an additional major metabolic stress[2–6] in these already fragile patients. This combination of factors results in poor growth, with hypoplastic left heart syndrome patients being the most severely affected. Malnutrition and growth failure in neonates are a powerful risk factor for increased morbidity and mortality, including poor neurobehavioral development.[7]

Effective therapy for correcting malnutrition and growth failure in neonates would be expected to improve outcomes following surgical repair of CHD. Several approaches to improve growth, including early parenteral nutrition, prompt initiation of enteral feeds, and traditional feeding protocols, have shown inconsistent results.[8–10] We recently demonstrated the potential of oxandrolone to decrease weight loss following surgical repair of CHD.[11] Oxandrolone is an orally available anabolic steroid that binds to androgen receptors, promoting protein synthesis. The clinical util-

Table 1. Long-Term Stability of Oxandrolone in Medium-Chain Triglyceride (MCT) Oil When Protected From Light*

Day	Glass Vials, %				Polyethylene Terephthalate Vial, %
	A	B	C	D	P†
1	100	100	100	100	100
2	101	102	95	91	109
7	82	100	85	90	95
22	81	96	86	86	96
30	96	106	103	99	112

* Data are normalized to concentration on day 1.

† A single preparation of oxandrolone in MCT oil was divided into 5 aliquots. Samples A–D were stored in glass amber vials, whereas sample P was stored in a polyethylene terephthalate vial.

ity of oxandrolone is well documented with regard to preventing weight loss and retaining lean body mass in chronically ill and severely injured patients.[12–14] In the pediatric population, oxandrolone has been introduced into the management of burn patients to improve wound healing, HIV patients to prevent muscle wasting, and patients with Turner syndrome to increase adult height.[15–22] In a previous clinical study, we found that oxandrolone administered as an extemporaneous compounded product in medium-chain triglyceride (MCT) oil demonstrated the greatest improvement in weight- and height-for-age *z* score compared with the untreated historical control patients and patients treated with oxandrolone prepared in aqueous solution.[11] Given the lipophilic nature of steroids, we hypothesized that the improved effect generated by the MCT oil formulation may be due to improved solubility and stability of oxandrolone in the lipid-based vehicle.

In this study, we sought to define the formulation stability and the pharmacokinetic characteristics of the extemporaneous MCT oil preparation to better understand its use in reducing growth failure following surgical repair of complex CHD in neonates.

Materials and Methods

Stability of Oxandrolone. ***Preparation of Oxandrolone in MCT Oil.*** The Primary Children's Hospital compounding pharmacy prepared oxandrolone in MCT oil. Four 2.5-mg oxandrolone tablets (10 mg total, PAR Pharmaceuticals, Chestnut Ridge, NY) were triturated using a ceramic mortar and pestle. A 1.5-mL aliquot of MCT oil was then added to the mortar, and it was levigated to produce a smooth suspension. The suspension was then transferred into a graduated glass cylinder. The pestle was then rinsed into the graduated cylinder an additional 4 times, with MCT oil volumes between 1.5 and 2.0 mL, to a total volume of 10 mL. This process yielded an oxandrolone concentration of 1 mg/mL. The suspension was then transferred to a glass container, and it was vortexed for 5 minutes to homogenize the oxandrolone solution. Subsequently, the solution was centrifuged (Hettich EBA20, Hettich Instruments, Beverly, MA) at 3000 rpm (2000 × *g*) for 30 minutes to pellet insoluble excipients present in the solution. The resulting supernatant was then decanted into an amber bottle and stored at room temperature (~20°C).

Analytic Method for Measuring Oxandrolone. A validated liquid chromatography–tandem mass spectrometry method has previously been described for determining oxandrolone concentrations.[23] Oxandrolone reference standard was purchased from Steraloids Inc (Newport, RI) and was used to prepare calibration standards and quality control samples. Briefly, oxandrolone was isolated from heparinized plasma using an *n*-butyl chloride–based liquid-liquid extraction. Samples were quantified on an instrument consisting of an Agilent 1100 series LC system (Agilent Technologies, Wilmington, DE) and a Thermo-Finnigan TSQ AM MS/MS (ThermoFinnigan, San Jose, CA). The dynamic range of the assay was between 2 and 200 ng/mL. For neonatal samples, the assay was adapted for use with 100-µL sample volume, to account for the limited blood volume available for collection from a neonatal population.

Stability. At a final volume of 10 mL, preparing oxandrolone into MCT oil yields sufficient volume for multiple doses. We therefore evaluated the stability of the oxandrolone preparation when stored, as well as the potential for photodegradation of oxandrolone in the formulation. The above-described analytic method was used to quantify oxandrolone in each sample. For all tested conditions, instability was defined as a change in concentration greater than ±15% from the control sample. The 15% criterion is based on acceptability criteria associated with the bioanalytic assay.

First, a 25-mL (using ten 2.5-mg oxandrolone tablets) volume of the oxandrolone in MCT oil was prepared as described, and it was evenly aliquoted (5 mL) into 5 separate amber vials. Four vials were glass (vials A–D), and the fifth vial was plastic (polyethylene terephthalate, vial P). The vials were stored in a drawer (to prevent photodegradation) at ambient conditions. Samples from each vial were taken on days 1 (control), 2, 7, 22, and 30.

Table 2. Effect of Light on the Stability of Oxandrolone in Medium-Chain Triglyceride (MCT) Oil When Stored in a Syringe*

Hour	Light, %			Dark, %		
	A	B	C	D	E	F
0	92	96	93	95	99	104
24	100	93	95	97	90	96
48	82	86	90	94	88	96
72	89	86	86	93	99	99

* Data are normalized to a control sample from an amber vial that was analyzed immediately after preparation.

Next, a 5-mL (using two 2.5-mg tablets) volume was prepared, and it was drawn (0.5 mL) into each of six 1-mL syringes (syringes A–F). Syringes A to C were capped and stored on the benchtop, whereas syringes D to F were capped and stored in a drawer to protect against photodegradation. The remaining volume of oxandrolone was transferred to an amber vial, where it was stored in a drawer and was used as the control sample. The vial and all syringes were held at ambient temperatures. A sample from each syringe was taken every 24 hours, and it was compared to a single sample obtained from the amber vial immediately after preparation.

Pharmacokinetics of Oxandrolone in MCT Oil. ***In Neonates.*** We previously described a single-center, prospective, open-label pilot trial of oxandrolone in neonates following surgery to repair complex CHD.[11] This study consisted of 4 cohorts, with the final cohort in the study receiving oxandrolone in MCT oil via the buccal mucosa at a dose of 0.1 mg/kg/day administered once daily for 30 days following surgery. An additional 5-patient cohort, whose data were not previously published, received oxandrolone in MCT oil in the buccal mucosa at a dose of 0.2 mg/kg/day administered twice daily. The MCT oil preparation was measured and delivered to the buccal mucosa via a polypropylene oral syringe. Intensive blood samples were collected on days 3 and 14 (before dose, 30 minutes, 1 hour, 3 hours, 7 hours, and 11 hours), and a single predose sample was collected on days 7 and 28. Blood was collected into 0.6-mL collection tubes with heparin as an anticoagulant at each time point. Plasma was isolated by the clinical laboratory and was stored at −80°C until assayed.

Relative Bioavailability—Adults. In light of the variability in the observed neonatal pharmacokinetic data that were previously published, we also evaluated the relative bioavailability of the MCT oil formulation in an adult male population. This enables us to determine if the variability was drug, formulation, or population dependent. Data for this study were collected as part of a University of Utah crossover study in healthy adult males. After an overnight fast, participants received 0.1 mg/kg oxandrolone either as an oral tablet or in the MCT oil. Two weeks after the initial dose, participants received the alternate formulation, with the order of administration being randomized. MCT oil was delivered to the buccal mucosa (as was done in the neonates) for a total of 5 minutes. Participants were not allowed to drink for 30 minutes following the buccal administration. Blood samples were collected at 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours, and 48 hours after dose, with a greater than 7-day washout period between administrations. Collected samples were quantified and pharmacokinetic analysis completed as described above.

Pharmacokinetic Analysis. Assessment was performed using the non-compartmental analysis toolbox of Phoenix WinNonLin v8.1 (Certara USA, Inc; Princeton, NJ). The linear up-log down calculation approach was used, and the elimination slope was allowed to be best-fit by the software. Given the dynamic nature of neonatal growth and metabolic maturity, data from day 3 were analyzed separately from day 14 data to determine pharmacokinetic parameters.

Results

Stability of Oxandrolone in MCT Oil. Because a single preparation of oxandrolone in MCT oil yields sufficient volume for multiple neonatal doses, we evaluated the long-term stability of the preparation. On average, oxandrolone concentrations were within ±13% of control (day 0) concentrations when stored in amber glass vials for 30 days. Glass vial A deviated beyond the ±15% acceptance criteria on days 7 and 22; however, this sample was within acceptance criteria at day 30. No other samples exceeded acceptance criteria. In general, values on days 7 and 22 were lower than the other days that were tested, which may indicate that these values were driven by assay performance on those days, as opposed to an issue with stability, as concentrations in the glass vials were found to be within ±6% of the expected concentration at day 30 (Table 1). Moreover, bioanalytic quality control concentrations analyzed in the same batch as day 7 and 22 samples were about 6% to 9% lower than historical values and those analyzed alongside day 1, 2, and 30 samples. These results demonstrate that oxandrolone is stable in MCT oil for at least 1 month when stored at ambient conditions in glass or plastic amber vials and protected from light exposure.

Table 3. Calculated Neonatal Pharmacokinetic Parameters

Participant #	Day 3			Day 14		
	t½, hr	C_{max}, ng/mL	AUC, ng·hr/mL	t½, hr	C_{max}, ng/mL	AUC, ng·hr/mL
Administered once daily						
1	2.26	11.4	21.6	1.98	31.9	65.7
2	3.14	39.0	63.0	2.49	8.85	21.3
3	3.87	28.6	84.5	2.37	21.8	90.1
4	2.81	32.9	82.4	2.29	32.2	77.5
5	2.28	2.99	13.0	1.01	42.0	66.8
Average (%CV)	2.87 (23)	23.0 (66)	52.9 (64)	2.03 (30)	27.4 (46)	64.3 (40)
Administered twice daily						
6	3.44	26.7	80.8	0.915	28.4	50.0
7	1.73	13.0	24.0	0.918	25.1	40.2
8	1.56	8.29	32.7	2.04	11.7	22.5
9	2.03	17.1	20.3	1.42	8.20	24.9
10	2.19	10.5	26.4	5.05	2.73	15.0
Average (%CV)	2.19 (34)	15.1 (48)	36.8 (68)	2.07 (84)	15.2 (73)	30.5 (47)

C_{max}, maximum concentration; t½, half-life

In general, oxandrolone was stable at 72 hours in glass syringes maintained at ambient conditions on the benchtop (−14%) and in a drawer (−7%; Table 2); however, samples exposed to light (ie, benchtop) trended towards degradation. Additionally, one of the samples stored on the benchtop exceeded the acceptance criteria (−18%) at 48 hours. These data indicate that storage of oxandrolone on the benchtop for longer than 48 hours created an unacceptable risk of instability. Thus, although oxandrolone in MCT oil can be stored on the benchtop for up to 24 hours, the preparation should be protected from light to decrease the risk of photodegradation.

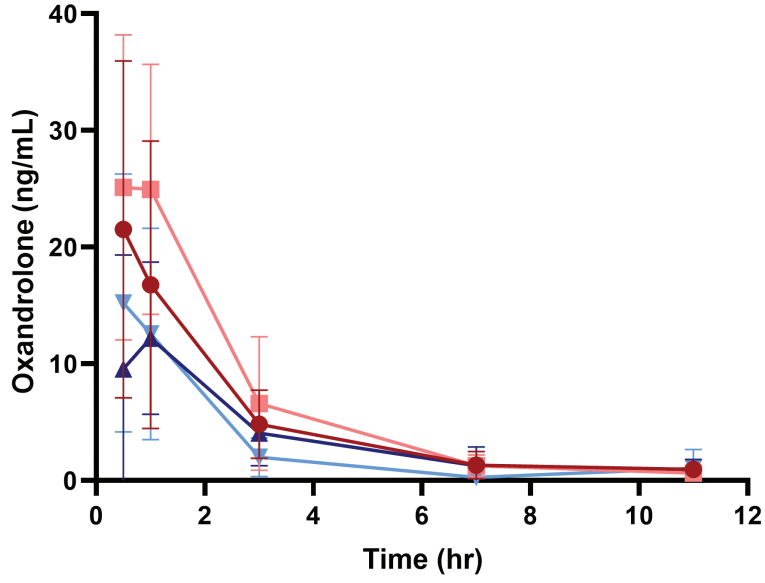
Pharmacokinetics of Oxandrolone in MCT Oil. ***In Neonates***. Ten neonates received oxandrolone in MCT oil to the buccal mucosa following surgical repair of CHD. The median (range) age and weight at enrollment were 4.5 days (1–12 days) and 3.5 kg (2.1–4.2 kg), respectively. Most of these neonates were male (9 of 10), and all but one was white. The first 5 received oxandrolone once daily (0.1 mg/kg/day), whereas the other 5 received twice-daily oxandrolone (0.2 mg/kg/day). Elimination half-lives were similar between days 3 and 14, and between the once- and twice-daily arms (average [%CV]: 2.3 [45%] hours; Table 3). Oxandrolone was rapidly absorbed, with a median time to peak concentration of 1 hour (Figure 1). Average (%CV) peak concentrations were 17.3 (48%) ng/mL in the twice-daily arm, whereas the same values for the once-daily arm were 25.2 (53%) ng/mL. The average (%CV) $AUC_{0\text{-inf}}$ values were 58.6 (49%) and 36.9 (55%) ng·hr/mL in the once- and twice-daily dosing arms, respectively.

In Adults. A total of 6 adult male participants were enrolled in the study, and each received between 7.5 and 10 mg of oxandrolone in both the oral tablet and buccal MCT oil arms of the study. The median (range) age and weight for these participants at enrollment were 28.5 years (20.8–35.8 years) and 84.5 kg (70.1–101 kg), respectively. Average (%CV) peak concentrations were 67.6 (101%) ng/mL and 44.6 (87%) ng/mL in the oral tablet and MCT oil arms, respectively (Table 4). Peak concentrations largely occurred at 1 hour after dose in both arms of the study. All 48-hour samples were below limit of quantitation (Figure 2). Half-lives in both formulations were similar, but they were longer than those observed in the neonatal population, with an average (%CV) half-life of 6.7 (70%) hours in the MCT oil formulation. Average (%CV) AUC values were 483 (51%) and 249 (63%) ng·hr/mL for the oral tablet and MCT oil, respectively. Bioavailability ranged between 8.5% and 93.8%, with an average value of 62.5%. A total of 4 of the 6 participants had bioavailability of ≥63.9%, indicating that the buccal mucosa successfully absorbed most of the administered oxandrolone relative to the oral tablet. It is unclear why the bioavailability of the MCT oil formulation was lower in the remaining 2 participants. However, these 2 participants represent the highest oral tablet AUC values, and the participant with a bioavailability of 8.5% had the lowest MCT oil (74 ng·hr/mL) AUC.

Discussion

Oxandrolone in MCT oil has demonstrated potential for improving neonatal growth following complex surgical repair of CHD. Evaluating the stability of this

Figure 1. Mean ± SD oxandrolone concentrations on days 3 and 14 following buccal administration of a medium-chain triglyceride (MCT) oil formulation once (QD) and twice (BID) daily in neonates after a surgical congenital heart defect repair.



extemporaneous formulation and understanding the pharmacokinetics of oxandrolone following administration to the buccal mucosa represent vital steps to determining the clinical utility of this administration route.

Stability. We previously evaluated the effectiveness of oxandrolone in a variety of formulations and administration routes (aqueous vs MCT oil and oral or nasogastric tube vs buccal mucosa). In that analysis we determined that the aqueous preparation of oxandrolone yielded a suspension that was prone to precipitate, likely due to the lipophilic nature of the drug. Additionally, we hypothesized that the observed pharmacokinetics variability resulting from nasogastric administration was a result of oxandrolone adhering to the nasogastric tube. We therefore selected an MCT oil formulation of oxandrolone administered to the buccal mucosa, to minimize the variability in drug exposure observed in the orally administered aqueous formulation. The MCT oil formulation demonstrated greater solubility than the aqueous formulation, and it yielded the greatest benefit to weight gain in our pilot study,[11] leading us to further evaluate the clinical potential of this formulation.

For oxandrolone in MCT oil to have widespread clinical utility, the formulation must remain stable when stored, especially given the small volume needed for administration in a neonatal population. We therefore evaluated the stability of oxandrolone as a function of both time since preparation and exposure to light. We determined that the formulation was stable for up to 1 month following preparation when stored at ambient conditions in glass or plastic amber vials and protected from light. Exposure to light hastened the degradation of the compound, rendering it unacceptable for use after 48 hours of storage. Notably, we did not observe any change in color or pH of the formulation during stability testing, nor was there microbial growth after 180 days when stored in the dark (data not shown). As a result, we suggest precautions against photodegradation, such as storing the preparation in an amber vial and in a dark space.

Pharmacokinetics. Drug administration in neonates is limited by the inability to swallow solid formulations; therefore, alternate approaches are needed. One common approach is to administer the drug in a suspension via feeding tube; however, our early experience pointed to the likelihood that feeding tube administration resulted in variability in the amount of drug that was delivered successfully. We instead attempted to deliver it to the buccal mucosa, which has previously been described as a feasible site for steroid delivery in healthy adults.[24] Furthermore, a study in rats found that the corticosteroid prednisolone was more bioavailable when administered via a buccal film than via oral suspension.[25] Although buccal administration of oxandrolone resulted in improved maintenance of patient weight,[11] our pharmacokinetics study demonstrated extensive variability in systemic exposures in these neonates. Furthermore, observed concentrations in our neonatal population were substantially lower than

Table 4. Calculated Pharmacokinetic Parameters From the Adult Bioavailability Study

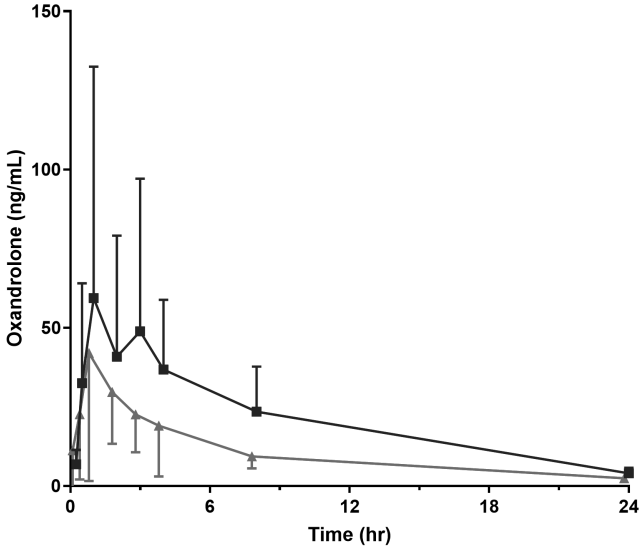
Patient	Formulation	C_{max}, ng/mL	T_{max}, hr	AUC_{inf}, ng·hr/mL	F, rel, %
1	Tablet	31.0	1.0	206	
	MCT oil	18.9	3.0	191	92.4
2	Tablet	33.4	4.0	451	
	MCT oil	41.8	0.5	288	63.9
3	Tablet	17.1	1.0	227	
	MCT Oil	12.9	4.0	171	75.3
4	Tablet	47.7	2.0	580	
	MCT oil	46.5	1.0	240	41.3
5	Tablet	201	1.0	866	
	MCT oil	28.2	2.0	74	8.5
6	Tablet	75.5	0.5	567	
	MCT oil	119	1.0	532	93.8
Average (%CV)	Tablet	67.6 (101)	1.6 (81)	483 (51)	
	MCT oil	44.6 (87)	1.9 (71)	249 (63)	62.5 (53)

C_{max}, maximum concentration; CV, coefficient of variation; MCT, medium-chain triglyceride; T_{max}, time to maximum concentration

previous reports of oxandrolone,[26,27] although all prior studies were conducted in adult males. Importantly, previous reports of oxandrolone concentrations have varied significantly, with exposures that potentially depend upon the dosage form administered (ie, concentrations from a 1 × 10 mg dose are not equivalent to administering 4 × 2.5 mg tablets).[27,28]

We therefore conducted a crossover bioavailability study in adult males. The purpose of this study was 2-fold. The first aim was to establish the bioavailability of our MCT oil preparation administered via the buccal mucosa relative to oral administration. Our results from this aim show that the MCT oil is well absorbed through the buccal space, with most (4 of 6) patients having a bioavailability >60%, and 2 patients having bioavailability >90%. The variability in observed bioavailability does indicate the need to further understand the physiologic parameters that may contribute to the success of this route of administration. The second aim of this study was to establish concentrations expected from an

Figure 2. Mean ± SD oxandrolone concentration following medium-chain triglyceride (MCT) oil and oral tablet administration in adult males.



■ Tablet; ▲ MCT

adult male population, so as to understand if the lower exposures (relative to literature using a 10-mg tablet) observed in our neonatal population were a result of the formulation and route of administration, or a characteristic of the studied population. The average AUC from the adults receiving MCT oil was approximately 5-fold higher than the neonates, when both received a 0.1 mg/kg dose. This result, in combination with the finding that oxandrolone in MCT oil is generally well absorbed through the buccal mucosa, indicates that the lower pharmacokinetic values observed in the neonates is likely a characteristic of the population. It is well established that children, especially infants, exhibit pharmacokinetics that are distinct from adults, in part due to differences in metabolic capacity.[29,30] It can be expected, therefore, that a neonatal population, especially one with such compromised and diverse metabolic capacity as our postoperation cohort,[1–6] can have exposures that differ greatly from the reported adult male pharmacokinetic data. It is therefore imperative to establish oxandrolone concentrations specific to this unique population which are associated with improved weight gain following surgical CHD repair via targeted clinical studies.

Conclusion

Oxandrolone in MCT oil is stable for at least 1 month at room temperature when protected from conditions that could lead to photodegradation. Regardless of the route of administration, the pharmacokinetics of oxandrolone are highly variable in both neonates and adults. Decreased exposure to oxandrolone in the neonate following CHD repair is likely a characteristic of the population, and not a result of the MCT oil formulation nor of the buccal mucosa route of administration. These results support the further evaluation of oxandrolone in MCT oil to limit weight loss following complex surgical repair of CHD.

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Ethical Approval and Informed Consent The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at the University of Utah/Intermountain Healthcare/Primary Children's Hospital (00041510 and 00099086). All patients and/or parents/caregiver(s) provided written informed consent and/or assent (as applicable) at enrollment.

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