CASE REPORT

Successful Treatment of a Seizure Disorder with Chronic High-Dose Chloral Hydrate:

A pediatric case report

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INTRODUCTION

Chloral hydrate (CH) has been used as a sedative hypnotic for over a century. It was synthesized in 1832, and Liebreich first reported its use as a hypnotic in 1869 (1). In recent years, newer hypnotics, such as benzodiazepines, have largely replaced CH due to decreased potential toxicities (2). Reports of chloral-hydrate-induced arrhythmias exist (3, 4). Theoretical long-term risks of carcinogenicity are also of concern (2, 5, 6). Today, CH is primarily used in pediatrics. Due to its minimal effects on respiration, the drug is often used by neurologists as a sedative during diagnostic exams that require a child to lie still or by dentists during uncomfortable procedures (7). Although noted by Leibreich in 1869 for its anticonvulsant properties, CH is not often used to treat seizure disorders in humans (1). Its use was reported by Krsek and colleagues in a child with Ohtahara syndrome at a dose of 58 mg/kg per day after conventional anti-epileptic drugs had failed (8). Enoki and colleagues also reported using CH as a single dose (41.7-62.5 mg/kg) for clustering seizures in benign convulsions with mild gastroenteritis (9). In a review of treatment of status epilepticus, Walker and Teach refer to an audit published by Hindley and colleagues in which CH (10-30 mg/kg) was used as a first- and/or second-line agent to control seizures in patients with known seizure disorders (10, 11).

Here we report the use of CH as a sedative that we suspect has controlled a seizure disorder in a patient at Roger's House, a pediatric palliative care facility associated with the tertiary pediatric Children's Hospital of Eastern Ontario (CHEO).

CASE REPORT

R.F. is a 12-year-old male with a history of mitochondrial myopathy, complex III deficiency, and marked developmental delay. He has mixed central and obstructive sleep apnea, for which he has had a tracheostomy since the age of two. At 20 months of age, R.F. was started on CH 250 mg (70 mg/kg) every four hours as needed for refractory agitation. Soon thereafter, he was scheduled to take this dose every day at bedtime for insomnia. Over the years, his CH dose was increased to control his insomnia. By age 10, he was taking 3 g (83 mg/kg) of CH at bedtime. R.F. also has a history of seizures, but had not had a seizure from ages 7 to 10.

When R.F. was 10, his family relocated. He was noted to be on a high dose of CH in late January of 2007. He was transferred to our centre, but data for monitoring for long-term effects of high-dose CH were not available from the previous centre. The health care team decided that his dose of CH should be reduced to avoid potential toxicity, although there was no toxicity manifest. Alternatives were also reviewed. CH was decreased from 3 g at bedtime to 2.3 g (64 mg/kg) on February 9, 2007, and further to 2.1 g (58 mg/kg) on February 14, 2007. During this time, R.F. was noted to have numerous seizures, with periods of grimacing, moaning, and crying throughout the night. By February 28, R.F. was on phenobarbital 30 mg twice daily to control the seizures attributed to CH withdrawal. Over the following weeks, seizures continued. On the advice of the neurologist, R.F. was admitted to our tertiary care institution for seizure control on April 5, 2007, where his CH dose remained constant at 2.5 g (69 mg/kg) at bedtime. Several anticonvulsants were

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used, including lorazepam, diazepam, levetiracetam, clonazepam, and phenobarbital. On four occasions, these medications failed to break the seizure, and 10 ml of paraldehyde was administered rectally during his stay in the CHEO pediatric intensive care unit. Melatonin was also introduced to try to help him with insomnia. Once stabilized, R.F. was discharged from our tertiary care institution. He left on April 13, 2007 with the following medications: CH 2.5 g at bedtime (to be weaned), tobramycin 60 mg twice daily, diazepam 2 mg (to be weaned), lorazepam 1 mg (to be weaned), levetiracetam 500 mg once daily, phenobarbital 75 mg at bedtime, clonazepam 1.5 mg at bedtime, and melatonin 1 mg at bedtime.

R.F.'s mother contacted the neurologist on call at CHEO on April 26, 2007 to report her son's increased wakefulness. The problem was not sleep induction but waking after five or six hours of sleep with some posturing or dystonia. His mother was instructed to leave the CH dose at 1 g at bedtime and to increase the bedtime dose of melatonin from 1 mg to 3 mg. Also, if her son continued to awaken after five or six hours of sleep for the next few nights, she could give him an extra 500 mg of CH to try to re-induce sleep. R.F.'s mother gave the extra 500 mg after two nights of only five or six hours of sleep and reported that sleep was not induced. She gave him 2 g of CH the following night to try to return him to the dose that allowed him to sleep through the night. His family physician then continued R.F. on 2 g at bedtime. Working closely with his mother, R.F.'s family physician increased his CH by 0.25 g a day, one day at a time, to treat his recurrent insomnia. This continued over several months, until the patient was stable at 3 g a day (76 mg/kg), in the fall of 2007. R.F. would later undergo a period of rapid growth, requiring a dose increase to 3.5 g a day (78 mg/kg).

Since the modification of his CH dose in early 2007, R.F. has been hospitalized twice for increased seizure activity: in January 2009 and June 2009. His CH dose of 3.5 g (78 mg/kg) was not changed during or between admissions. The neurologist and the palliative care team have decided to continue R.F. on this dose of CH to treat his insomnia and seizure disorder simultaneously.

DISCUSSION

In addition to helping R.F. sleep through the night, CH was found to be a useful adjunctive treatment for controlling his nighttime seizures when other treatments failed. R.F. is not alone in receiving this treatment for seizure control. Several cases of treatment with high-dose CH have been reported in the literature (1, 12). Powell and Rosenbloom reported two cases of high-dose CH treatment in pediatric patients (12). In the first case, an eight-year-old female with refractory epilepsy was initiated on CH for sedation at a dose of 20 mg/kg every two hours (240 mg/kg per day) and later increased to 30 mg/kg (360 mg/kg per day). The frequency of her seizures decreased within the first 24 hours of treatment, and they stopped completely after 48 hours. Much the way it was for our patient, CH was initiated for sedation only to emerge as an effective anticonvulsant. Her dose of CH was later reduced to 15 mg/kg every four hours (90 mg/kg per day) due to anorexia. Later bouts responded well to temporary increases to 30 mg/kg every two hours (360 mg/kg per day) but became increasingly refractory over the following six months. The patient eventually underwent a partial right hemispherectomy to remain seizure-free. The second case presented by Powell and Rosenbloom had similarities to their first case and to our own. CH was again initiated for sedation and accompanied by convenient anticonvulsive side effects. The CH dose was started at 30 mg/kg every three hours (240 mg/kg per day), with convulsions ceasing after 24 hours. After four days, the dose was decreased to 30 mg/kg every four hours (180 mg/kg per day). This patient, however, remained on CH for five months, up to the time of the Powell and Rosenbloom report. Although both patients presented by Powell and Rosenbloom were on doses similar to or greater than those of our patient, neither continued treatment for as long.

More recently, Pranzatelli and Tate reported four patients taking CH as an adjuvant treatment for monoclonus epilepsy; all were taking multiple anti-epileptic drugs (1). The first was a 32-year-old male who had been taking CH for 14 years. He would usually receive 1 g per day, but, depending on the severity of his myoclonic jerks, he would take a maximum of 3 g in a 24-hour period. Although this patient usually only received 1 g per day, his length of treatment was much closer to that of our patient. Also, his daily maximum of 3 g was close to the 3.5 g per day that our patient receives. Comparing the doses based on weight is difficult, as Pranzatelli and Tate did not report the weights of their patients (1). The second patient in the case series, a 35-year-old male, was placed on 1000-1500 mg of CH per day approximately 15 years after disease onset and had been taking CH for four years at the time of writing. CH at bedtime improved his sleep and monoclonus. Unlike our patient, he would later require CH during the day as well. The third patient, a 35-year-old female, required a 1 g dose twice daily to control monoclonus. The CH reduced her convulsions up to 75 percent and allowed her to travel. The fourth

patient was a 14-year-old female, much closer in age to R.F. She required a 500 mg dose three times a day to help control her daytime monoclonus. Before starting CH, her muscle jerking interfered with her school work and mobility; now she can attend school and visit public places without becoming sleepy. Similar to our patient, all four patients reported by Pranzatelli and Tate have taken CH chronically, with the briefest duration of treatment being five months (patient 3). In none of the four cases was the CH self-administered (1). Caregivers came to rely on CH to relieve monoclonus provoked by stressors such as public outings. Although R.F. does not use CH on an as-needed basis, his mother (and primary caregiver) remains one of the strongest advocates for keeping him on this dose of CH. Many similarities exist between the doses and the duration and effectiveness of treatment for the patients in this study and our own patient; however, to the best of our knowledge, R.F. is still on the highest chronic per-kilogram dose reported in the literature.

The decision to keep R.F. on the high dose of CH was complicated by theoretical and potential toxicities of the drug (3, 4, 6). Many physicians are hesitant to prescribe CH for chronic use due its potential carcinogenicity, yet little human data exists. Cardiotoxicity has been reported primarily from overdose (3), and CH use is not recommended in hepatic impairment due to its rapid metabolism to trichloroethanol by the liver (13). In light of these potential toxicities, R.F. continues to undergo regular echocardiograms and liver enzyme monitoring, neither of which has yielded a result that would suggest CH toxicity. The cognitive or behavioural impact of long-term use of CH in this child is difficult to assess, given his baseline severe developmental delay. The behavioural results of decreasing the medications were demonstrated by the family distress, which became apparent during the weaning process.

The second patient in the Powell and Rosenbloom report experienced hallucinations that settled without intervention (12). Although difficult to assess in our patient due to his developmental status, hallucinations have not been attributed to CH use. Pranzatelli and Tate observed "no problematic effects" from the use of CH in four patients, including the case of 14-year use (1). This patient did require dose escalation over the years, however, suggesting tolerance much like R.F.'s. The other three patients in the study did not show signs of tolerance, given that their doses could be reduced or stopped during times of less disease activity. CH infrequently produced a "sedate look" in the third patient in the Pranzatelli and Tate report, but it usually did not make her drowsy (1). In fact, the authors reported that the sedative effect of the drug was overall less than expected. The same patient was also the only one to report a burning sensation in the throat upon administration of the oral liquid; this was not reported by our patient, who has a gastrostomy tube for feeds and medications. The potential toxicity of the drug will be weighed against its ability to treat R.F.'s seizures, and he will continue on his current dose unless evidence of toxicity emerges.

In this case, CH has been successful in masking a suspected underlying seizure disorder in a pediatric patient. Although the dose is high (78 mg/kg), other reports of high-dose CH for seizure control do exist. Few reports, however, document its use chronically on the basis of theoretical carcinogenicity and other adverse effects, and little data exists on the effects of chronic administration. We suggest that CH be considered for seizure control when conventional anticonvulsant drugs are not effective. Chronic CH use in this pediatric case has considerably improved the quality of life of our patient.

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