# Anaesthetic considerations in the Prader-Willi syndrome: REPORT OF FOUR CASES

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*The anaesthetic management of four paediatric patients with the Prader-Willi syndrome is reported. The syndrome is characterized by obesity, mental retardation, genital hypoplasia, hypotonia, and diabetes mellitus. All patients were anaesthetized with halothane. Succinylcholine or pancuronium were used for muscle relaxation, without evidence of abnormal response. Common anaesthetic difficulties in this syndrome are obesity, hypotonia, disturbance in thermoregulation, arrhythmias, diabetes mellitus and convulsions.*

**Key words**

ANAESTHESIA: paediatric; Prader-Willi syndrome.

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The Prader-Willi syndrome is a syndrome characterized by obesity, mental retardation, genital hypoplasia, hypotonia and diabetes mellitus. Few anaesthesia case reports[1–5] have been published concerning this syndrome (Table I). We report the anaesthetic management of four patients with Prader-Willi syndrome.

## Case reports

Patient 1: 7-month-old male, weight 6.7 kg, height 66 cm.

At birth, the baby was mildly asphyxiated and had stridor. The body temperature was elevated, and the sucking reflex was weak, resulting in poor weight gain. The baby suffered from pneumonia at one month of age, at which time the diagnosis of Prader-Willi syndrome was made. Frequent episodes of fever occurred with persistent stridor.

At 7 months, the patient again developed pneumonia as well as atelectasis of the right upper lobe and high fever. The decision was made to aspirate retained pulmonary secretions, under general anaesthesia.

The patient was hypotonic, with cryptorchidism. The heart rate was 140, temperature 38.7° C. No premedication was administered. Anaesthesia was induced and maintained with halothane and oxygen. The trachea was intubated with the aid of succinylcholine 5 mg i.v. Succinylcholine (5 mg) was given i.v. twice during bronchoscopy. No prolongation of action of the muscle relaxant, or arrhythmias, were observed.

Postoperatively, occasional episodes of dyspnoea and cyanosis with fever (39° C) occurred for two days. By the seventh postoperative day, the general condition improved, but the patient died following convulsions and respiratory arrest on the 52nd postoperative day.

TABLE Anaesthesia cases of Prader-Willi syndrome

| *Reporter* | *Age (year)* | *Sex* | *Weight (kg)* | *Height (cm)* | *Operation* | *Anaesthetic agent* | *Muscle relaxant* | *Induction* | *Remarks maintenance* | *Postop. period* |
|---|---|---|---|---|---|---|---|---|---|---|
| Milliken *et al.*[1] | 10 | M | 42 | 130 | bil. orchidopexy (cancelled) | halothane | ? | — | tachycardia (250/min) PVC's | tachycardia PVC's |
| | 10 | M | 42 | 130 | bil. orchidopexy | halothane pethidine | succinylcholine 60 mg | hypertension (200/110 mm Hg) PVC's | PVC's bigeminy hypertension | PVC's |
| Palmer *et al.*[2] | 8½ | M | 31 | ? | bil. orchidopexy | halothane | ? | — | — | — |
| Yukioka *et al.*[3] | 3 | F | 11 | 81 | Open reduction (congenital dislocated hip) | halothane | None | — | — | fever GOT ↑ CPK ↑ |
| Noguchi *et al.*[4] | 12 | F | 50 | 138 | dental surgery | halothane | succinylcholine 40 mg | — | — | slightly delayed recovery |
| Yamaguchi *et al.*[5] | 3 | M | 17 | 87 | cleft lip repair orchidopexy testicular biopsy | halothane | None | difficult intubation | fever metabolic acidosis | fever |
| Yamashita *et al.* | 7 Mo. | M | 6.7 | 66 | bronchoscopy | halothane | succinylcholine total 15 mg | tachycardia (180/min) | tachycardia | fever dyspnea |
| | 8 | F | 40 | 121 | pacemaker implantation | halothane | succinylcholine 30 mg | Sick-Sinus syndrome | — | fever |
| | 10 | F | 70 | 132 | cholecystectomy | halothane | succinylcholine total 300 mg | PVC's | — | — |
| | 11 | M | 54 | 138 | bil. orchidopexy | halothane | pancuronium 1 mg succinylcholine 40 mg | — | — | fever |

Patient 2: 8-year-old female, weight 40 kg, height 121 cm.

Birth weight was 2640 g. Weight gain was poor due to weak sucking reflex. The patient was admitted to hospital because of dyspnea at the age of one year, eight months. Obesity was observed from the age of three years. At the age of seven, the patient began to have episodes of syncope, which required hospital admission. She was found to be suffering from the Prader-Willi syndrome as well as the sick-sinus syndrome, and the implantation of a pacemaker was scheduled.

Anaesthesia: the heart rate was 42 with irregularity, blood pressure was 124/70 mm Hg. Bradycardia, with incomplete right bundle branch block, was noted on the ECG. Anaesthesia was induced and maintained with halothane, nitrous oxide, oxygen. Succinylcholine 30 mg i.v. was given to facilitate endotracheal intubation. No additional muscle relaxant was administered during anaesthesia. The pacemaker was implanted uneventfully. The body temperature was stable throughout the procedure. Emergence from anaesthesia was uneventful, but low grade fever (37 to 38° C) was present for a week postoperatively.

Patient 3: 10-year-old female, weight 70 kg, height 132 cm.

Birth weight was 2700 g. The sucking reflex was weak from birth, and the baby was admitted because of poor weight gain. During this admission, several episodes of high temperature (to 40° C) of unknown aetiology were recorded. General development was slow, and the patient could not walk until two years, eight months. A polyphagic diathesis appeared at the age of three years and eight months, and a marked weight gain was noticed. The patient was admitted twice because of the unconsciousness of undetermined aetiology. Urine sugar was detected at the age of six, but no further examination or treatment was undertaken. At the age of ten, the patient was brought to the University Hospital for the evaluation and treatment of obesity, and the diagnosis of Prader-Willi syndrome was made. In the course of evaluation, jaundice appeared and gallstones were found. The patient was scheduled for cholecystectomy.

Preanaesthetic status: the patient was moderately mentally retarded, with a tendency to polyphagia and polydepsia. A high arched palate was present. The glucose tolerance test was abnormal. Left axis deviation was seen on the ECG, without arrhythmias.

Anaesthesia was induced and maintained with halothane, nitrous oxide, and oxygen. A transient episode of premature ventricular contractions, not requiring therapy, was observed at induction. The trachea was intubated with the aid of succinylcholine 40 mg i.v. Muscle relaxation was facilitated with intermittent i.v. administration of succinylcholine (total dose 300 mg). Cholecystectomy was performed uneventfully in one hour and 40 minutes. No prolonged effect of succinylcholine, elevation of plasma potassium levels or arrhythmias were observed during anaesthesia. Body temperature was stable throughout the operative course. Blood sugar was 7.2 to 9.9 mmol/l during the operation and no urinary ketone bodies were detected. Emergence from anaesthesia was uneventful, and postoperative course was smooth, without febrile abnormalities.

Patient 4: 11-year-old male, weight 54.0 kg, height 138 cm.

The patient was a product of fullterm normal delivery, with birth weight of 2650 g. Just after the delivery, weak crying with little body movement and hypotonia were observed. The baby was tube fed because of a poor sucking reflex. The patient could not walk until the age of one year, five months. At two years, six months of age, he was involved in a traffic accident, and subsequently the tendency to polyphagia and obesity developed. At the age of five, the patient was brought to the hospital for the evaluation of obesity, where the diagnosis of Prader-Willi syndrome with cryptorchidism was made. At age 11, he was admitted to have bilateral orchidopexy.

Preanaesthetic status: 11-year-old, obese with body mass index of 28.4, retarded, with I.Q. of 42. ECG and EEG were normal.

Anaesthesia was induced and maintained with halothane, nitrous oxide, and oxygen. The trachea was intubated with the aid of succinylcholine 40 mg i.v. following pancuronium 1 mg i.v. Bilateral orchidopexy was completed uneventfully. No prolonged effect of the muscle relaxants was observed. Emergence from anaesthesia was uneventful. The postoperative course was smooth with the exception of fever (to 38° C) on the first postoperative day.

## Discussion

In 1956, Prader *et al.*[6] described a new syndrome which they called "a syndrome of obesity, short growth, cryptorchidism, and mental retardation, with an amyotonia-like condition in the neonatal period". More descriptive titles than Prader-Willi syndrome have been suggested, such as "hypotonia, mental retardation, obesity, and cryptorchidism associated with dwarfism and diabetes in children,"[7] "hypogenital dystrophy with diabetic tendency,"[8] "congenital muscular weakness and hypotonia with mental retardation, defective development of the testicles, and obesity,"[9] "$H_2O$ syndrome, i.e. hypotonia, hypomentia, and obesity,"[10] and "syndrome of HHHO, i.e. hypotonia, hypomentia, hypogonadism and obesity."[11]

The course and natural history have been divided into two distinct phases.[11] The first phase is characterized by the amyotonia which is the leading manifestation during the newborn period and early infancy. In this period, marked hypotonia, poor sucking, swallowing and cough reflexes, a weak cry and sometimes episodes of asphyxia[12,13] are observed. Prolonged nasogastric tube feeding is frequently necessary.[14] In the second phase, hyperphagia, obesity, and hypogonadism are the essential manifestations. The Pickwickian syndrome or obesity hypoventilation syndrome develops in some patients.[11,15] There is little growth in height, and the patients remain of short stature. Some patients have difficulty in temperature control, with a tendency to hypothermia or hyperthermia.[12] They are mentally retarded in most instances, with I.Q.'s ranging from 20 to 80.[11] Bilateral cryptorchidism is reported to be present in more than two thirds of the male patients,[11] and orchidopexy is a common operation for these children. Diabetes mellitus is a late-appearing complication of the second phase.

Several abnormalities have been found to be frequently associated with this syndrome. Of interest to anaesthetists are micrognathia, high arched palate, scoliosis, congenital dislocation of the hip, strabismus, and hand and finger anomalies.[11] A straight ulnar border is one of the characteristics of the syndrome.[16] A high degree of enamel defects, dental decay, and caries are also frequently observed.[4,17]

The cause of this syndrome is unknown, but a disturbance in the hypothalamus has been postulated because of the various manifestations of the syndrome.[11] Recently, deletion of chromosome 15 was suggested as a cause of the syndrome.[18]

Several points appear to be important for the anaesthetic management of patients with this syndrome.

(1) Hypotonia: The hypotonia tends to disappear with age. The origin of weakness is not clear,[11] but muscle enzyme studies, electromyographs and muscle biopsies have shown no abnormalities.[7,19,20] With regard to muscle relaxants, no abnormal responses are reported with the patients in the second phase. Succinylcholine has been administered uneventfully[1,4] (Table I), and we have not experienced any abnormal responses, even with a total dose of 300 mg in patient 3.

Our patient 1 is the only reported patient who was given succinylcholine in the first phase of the syndrome. Again, no abnormal responses were observed, but muscle relaxants should be used cautiously, especially in patients in the first phase of the syndrome.

(2) Disturbance in thermoregulation: there are several reports of unexplained high fever or hypothermia (Table I).[5,11,12] Mininberg[21] described an apparent predisposition of children with this syndrome to anaesthesia-associated hyperthermia. Rapid rise of body temperature with metabolic acidosis during anaesthesia was reported by Yamaguchi *et al.*[5] (Table I). Rise of body temperature following operation was seen in our patients 1, 2 and 4, which agrees with the report by Yukioka *et al.*[3] (Table I). Although Bloom *et al.*[22] described similarities between the patient populations with malignant hyperthermia and this syndrome, the relation of this syndrome to malignant hyperthermia is not clear.

(3) Abnormalities of cardiovascular system: usually the cardiovascular system is not compromised,[11] but Dunn[23] reported isolated incidences of moderate hypertension and cyanotic episodes. Milliken *et al.*[1] reported premature ventricular contractions with high blood pressure during halothane anaesthesia which resulted in cancellation of the case (Table I). Our patient 3 also had transient premature ventricular contractions at induction. Patient 2 had the "sick sinus syndrome" (Table I).

(4) Obesity and diabetes mellitus: simple obesity is usual, but some patients have developed the Pickwickian syndrome[11] or obesity hypoventilation syndrome.[15] Such patients are likely to die from cor

pulmonale.[16] Diabetes mellitus develops at about ten years of age, but it is mostly the non-juvenile type, and is usually mild.[11,12,14]

(5) Convulsion: convulsion is also reported with the syndrome,[11,14] and the epileptogenic agents, such as ketamine or enflurane, should be used cautiously.

(6) Choice of anaesthetic agent: halothane is the only anaesthetic agent reported to be used with the syndrome[1–5] (Table I). Our four patients were also anaesthetized with halothane. Halothane appears to be a good choice because of (1) absent hyperglycaemic effect, (2) easy controllability (3) no epileptogenicity (4) easy respiratory control. With regards to cardiac arrhythmias, isoflurane might be a better choice. However, we have had no experience with isoflurane in this syndrome, nor have case reports of use of this agent in the Prader-Willi syndrome been published.

(7) Common operations required by patients with this syndrome include orchidopexy, dental surgery, repair of cleft lip or palate, strabismus surgery, and orthopaedic surgery for congenital dislocation of the hip or scoliosis.

Whenever the anaesthetist has a mentally retarded, obese, short-stature patient with a straight ulnar border presenting for the above operations, one should consider the possibility of the Prader-Willi syndrome.

## References


1 *Milliken RA, Weintraub DM.* Cardiac abnormalities during anesthesia in a child with Prader-Willi syndrome. Anesthesiology 1975; 43: 590–2.

2 *Palmer SK, Atlee JL, III.* Anesthetic management of the Prader-Willi syndrome. Anesthesiology 1976; 44: 161–3.

3 *Yukioka H, Kitamura E, Nagata N, Fujimori M.* Prader-Willi syndrome and anesthetic management. Jap J Anesth 1979; 28: 518–21.

4 *Noguchi I, Ebihara M, Nakajima H, Sekita S, Senda N, Amemiya Y.* Experience of anesthesia for a patient with Prader-Willi syndrome. J Jap Dent Soc Anesth 1980; 8: 56–62.

5 *Yamaguchi M, Okuya R, Nishijima H, Ishida H, Tamura T.* Anesthetic experience of Prader-Willi syndrome. J Clin Anesth 1981; 5: 411–4.

6 *Prader A, Labhart A, Willi H.* Ein syndrom von Adipositas, Klinwuchs, Kryptochismus und Oligophrenie nack Myatonieartigen Zustand im Neugemborenenalter. Schweig. Med. Wschr. 1956; 86: 1260–1.

7 *Laurance BM.* Hypotonia, mental retardation, obesity, and cryptochidism associated with dwarfism and diabetes in children. Arch Dis child 1967; 42: 126–37.

8 *Evans PR.* Hypogenital dystrophy with diabetic tendency. Guy Hosp Rep 1964; 113: 207–22.

9 *Ford FR.* Congenital muscular weakness and hypotonia with mental retardation, defective development of the testicles and obesity. In F.R. Ford (ed): Disease of the nervous system in infancy, childhood and adolescence. ed 5, Springfield, Ill.: Charles C. Thomas, 1966, pp. 36–7.

10 *Engel WK, Hogenhuis LAH.* Genetically determined myopathies-Conditions difficult to classify: $H_2O$ syndrome, in A.F. DePalmaled. Clinical orthopaedics and related research, No. 39, Philadelphia: JB Lippincott Co. 1965, pp. 54.

11 *Zellweger H, Schneider HJ.* Syndrome of Hypotonia-Hypomentia-Hypogonadism-Obesity (HHHO) or Prader-Willi syndrome. Amer J Dis Child 1968; 115: 588–98.

12 *Cohen MM, Jr, Gorlin RJ.* The Prader-Willi Syndrome. Amer J Dis Child 1969; 117: 213–8.

13 *Landwirth J, Schwartz AH, Grunt JA.* Prader-Willi Syndrome. Amer J Dis Child 1968; 116: 211–7.

14 *Hall BD, Smith DW.* Prader-Willi syndrome. A resume of 32 cases including an instance of affected first cousins, one of whom is of normal stature and intelligence. J Pediat 1972; 81: 286–93.

15 *Orenstein DM, Boat TF, Owens RP et al.* The obesity hypoventilation syndrome in children with the Prader-Willi syndrome: A possible role for familial decreased response to carbon dioxide. J Pediatrics 1980; 97: 765–7.

16 *Laurance BM, Brito A, Wilkinson J.* Prader-Willi syndrome after age 15 years. Arch Dis Child 1981; 56: 181–6.

17 *Foster SC.* Prader-Willi syndrome: report of cases. J Am Dent Assoc 1971; 83: 634–8.

18 *Ledbetter DH, Riccardi VM, Airhart SD, Strobel RJ, Keenan BS, Crawford JD.* Deletion of chromosome 15 as a cause of the Prader-Willi syndrome. N Engl J Med 1981; 304: 325–9.

19 *Dubowitz V.* Hypotonia-obesity syndrome (the Prader-Willi syndrome). Clin Dev Med 1969; 31: 65–73.

20 *Fraccaro M, Zuffardi O, Bähkler EM, Jurik PL.* 15/15 translocation in Prader-Willi syndrome. J Med Genet 1977; 14: 275–6.
21 *Mininberg DT.* Prader-Willi syndrome. Urologists' Correspondence Club, February 20 (1980).
22 *Bloodm DA, Iwamoto K, Reynolds RC, Ehrlich RM.* Management of malignant hyperthermia. J Urology 1981; 125: 594–7.
23 *Dunn HS.* Prader-Labhart-Willi syndrome – Review of the literature and report of 9 cases. Acta Paediatr Scand Suppl 1968; 186: 1–38.

Résumé

*On rapporte la conduite anesthésique de quatre patients présentant le syndrome de Prader-Willi. Ce syndrome est caractérisé par l'obésité, l'arriération mentale, l'hypoplasie génitale, l'hypotonie et le diabète mellitus. Tous les patients furent anesthésiés avec l'halothane. La succinylcholine ou le pancuronium ont été administrés comme curarisants et ne présentèrent pas de réponse anormale. Les difficultés anesthésiques de ce syndrome sont l'obésité, l'hypotonie, les troubles en thermorégulation, l'arythmie, le diabète mellitus et les convulsions.*