CARDIAC ARREST FOLLOWING INDUCTION WITH PROPANIDID

A Case Report

BY

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SUMMARY

A case is described of a severe reaction following the use of propanidid for induction of anaesthesia in a toxic young boy. The sequence of events that culminated in clinical cardiac arrest, the subsequent successful resuscitation, recovery, and investigations, are reported. Massive histamine release is thought to be the most likely cause of the observed phenomena, yet no satisfactory explanation can be given as to how this comes about.

Recent experiences in the use of propanidid, especially in sick children have brought to light a peculiar type of reaction, not reported in any of the earlier studies with this agent (Zindler, 1965; Radnay, 1965; Kay, 1969). This case adds further evidence to the possibility of adverse reactions occurring in any sick child who is given propanidid.

CASE REPORT

An 8-year-old boy, weighing 25 kg, was admitted on June 17, 1969, with a 6-day history of acute appendicitis that had progressed to abscess formation. He was one of five children, with no previous medical illness, no allergies or known idiosyncrasies, and no family history of any disease. The parents were Jehovah's Witnesses.

On admission he was a very sick and toxic little boy, dehydrated, pyrexial, and he had a haemoglobin of only 10.8 g/100 mL. Treatment was begun with intravenous fluids and ampicillin. Some 12 hours after admission, when fluid and electrolyte balance was restored, he underwent the first operation for drainage of his pelvic abscess. On this occasion he was given propanidid 200 mg for induction of anaesthesia. This was followed by suxamethonium 25 mg, to facilitate intubation. Anaesthesia was maintained using oxygen, nitrous oxide and halothane. Intermittent injection of suxamethonium 10 mg plus 10 mg was used to obtain muscle relaxation. The operation and anaesthetic passed uneventfully. His postoperative progress did not, however, proceed as expected. He remained pyrexial, and there was abdominal pain and tenderness. By the 12th day it was clear that the pelvic abscess had not been adequately drained because of loculation of the pus, and that a second operation would be required. He had been maintained in good fluid and electrolyte balance, but his haemoglobin remained low (10.8 g/100 mL), packed cell volume being 35 per cent. For the second operation, anaesthesia was induced with methohexitone 40 mg, followed as on the first occasion by suxamethonium 25 mg. Halothane was not administered at this time, as additional analgesia was obtained with pethidine 20 mg, and muscle relaxation was obtained with pancuronium bromide 1 mg. At the end of this procedure, lasting 40 minutes, reversal with atropine and neostigmine produced a rapid return to spontaneous respiration, and recovery was once again uneventful. Despite these two operative procedures, and treatment with antibiotics to which the organisms were sensitive, the infective process did not clear up; he remained pyrexial, and toxic, and it became necessary to undertake a third operation; this took place on the 17th day after admission.

Fluid and electrolyte balance were maintained; Na+ 133 m.equiv/1., K+ 4.9 m.equiv/1., Cl− 94 m.equiv/1., urea <10 mg/100 mL, haemoglobin 10.0 g/100 mL, packed cell volume 35 per cent. The temperature was 99.4°F, the pulse rate 112 beats/min and the blood pressure 110/60 mm Hg. In spite of his prolonged toxic state, the child himself was much more cheerful than for his previous operations. He was smiling and playing with his toys, and showed no distress at being told of his operation. As on both previous occasions, no premedication was given. He was so co-operative when he came to the theatre that he held the facepiece himself during pre-oxygenation.

Induction then began with the injection intravenously of a 5 per cent solution of propanidid. As the injection was proceeding, and when some 3 ml (150 mg) had been given, there was a sudden and quite dramatic change. He complained of severe abdominal pains, threw his arms and legs about in wild commotion, screamed with pain, then lay back unconscious. His colour now began to change with remarkable rapidity. At first his face became a bright glowing crimson, this spreading over his trunk and limbs, and his skin felt very "hot". He was now unconscious and apnoic; oxygen was administered through a facepiece and manual ventilation of the lungs commenced. Despite oxygen and adequate ventilation, his colour changed from bright crimson to a deep purple, then to a peculiar "blotchy" appearance; areas of deep cyanosis mixing with areas of blanched whiteness. His cheeks

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were a deathly white, while his lips, eyes, forehead and ears were deeply cyanosed. His trunk and limbs were covered in this strange mottling. The pulse became impalpable, no cardiac impulse could be felt, the pupils were widely dilated, and clinically the circulation was at a standstill: cardiac arrest was assumed. The time interval from first reaction to assumed cardiac arrest was a little under 2 minutes.

He was intubated and ventilated easily with 100 per cent oxygen, there being no suggestion of bronchospasm. External cardiac massage was commenced and, while an intravenous drip was being set up, 40 m.equiv of sodium bicarbonate was given through the needle that had somehow miraculously stayed in the back of his hand. Through the intravenous drip was given a further 60 m.equiv of sodium bicarbonate, then 120 ml of 20 per cent mannitol, 300 mg of hydrocortisone, followed by Hartmann's solution. While an e.c.g. was being collected and set up, a few sharp thumps on the chest were made with a fist. This manoeuvre proved to be efficacious. On replacing the hand over the chest for recommencing external cardiac massage, a clearly perceptible cardiac impulse could be felt. Now the radial pulses could be palpated, and almost immediately he began to make efforts at spontaneous respiration. It was now 8 minutes after the beginning of the reaction, or some 6 minutes after the diagnosis of clinical cardiac arrest. The e.c.g. showed a normal sinus rhythm with a rate of 120 beats/min; the blood pressure was recorded as 100/60 mm Hg. Although there had been no electrocardiographic confirmation of cardiac arrest, clinically there was no doubt that an effective circulation had ceased. Skin colour now rapidly improved, the pupils returned to their normal size, and the child was clearly beginning to wake up, making it very difficult to maintain manual intermittent positive pressure ventilation.

Because of the child's prolonged toxic state, and the many difficulties that would ensue because of the inability to use blood, it was decided to proceed with the operation to drain the pelvic abscess. Ventilation was continued now with a 50 per cent mixture of oxygen and nitrous oxide, and the abscess was drained without great difficulty, the procedure taking only 10 minutes. On discontinuing the nitrous oxide, the child rapidly woke up and removed the endotracheal tube. He was now fully alert and could talk clearly and rapidly. A few sharp thumps on the chest were made with a fist. This manoeuvre proved to be efficacious. On replacing the hand over the chest for recommencing external cardiac massage, a clearly perceptible cardiac impulse could be felt. Now the radial pulses could be palpated, and almost immediately he began to make efforts at spontaneous respiration. It was now 8 minutes after the beginning of the reaction, or some 6 minutes after the diagnosis of clinical cardiac arrest. The e.c.g. showed a normal sinus rhythm with a rate of 120 beats/min; the blood pressure was recorded as 100/60 mm Hg. Although there had been no electrocardiographic confirmation of cardiac arrest, clinically there was no doubt that an effective circulation had ceased. Skin colour now rapidly improved, the pupils returned to their normal size, and the child was clearly beginning to wake up, making it very difficult to maintain manual intermittent positive pressure ventilation.

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Three months later he was readmitted for appendicectomy. Propanidid was not given on this occasion and anaesthesia was uneventful except that a mild generalized "flush" developed after premedication with atropine. No evidence of the presence of a carcinoid tumour was found.

One week later, immunological investigations were performed, all of which proved inconclusive.

Skin patch tests were performed by impregnating gauze with 1 ml of the drug (propanidid), and then placing the patch on the skin of the upper arm. Gauze impregnated with methohexitone was used as a control on the opposite arm. The sites were observed after 5 minutes, 30 minutes, 4 hours, and 24 hours. No reaction was observed from either the drug or the control.

Intradermal tests. A small intradermal injection of 5 per cent propanidid 0.1 ml was given into the skin of the anterior surface of the forearm. A similar injection of saline was given into the opposite forearm. Only a small weal (less than 0.5 cm diameter) developed with the test drug, and this disappeared after 2 hours.

Passive transfer (Prasnisz-Kustner) test. 0.1 ml of the patient's serum was injected intradermally into two sites on the left forearm of the author. After 24 hours, 5 per cent propanidid solution 0.1 ml was injected into one site, and saline into the other. A small area of erythema developed almost immediately at the site where the propanidid had been injected, but this was never greater than 2 cm in diameter, and it had disappeared completely within 30 minutes. No reaction was observed at the control site.

Subsequent progress of the patient was steady and uneventful, and he was discharged home on July 18, 1969, 32 days after his admission.

DISCUSSION

Despite the reported disadvantages of cardiovascular depression (Dundee, 1965; Van Wyke and Kok, 1966; Johnstone and Barron, 1968; Conway, Ellis and King, 1968), the increased incidence of nausea (Dundee and Clarke, 1964), the prolongation of the action of suxamethonium (Clarke, Dundee and Daw, 1964; Howells et al., 1964; Clarke, Dundee and Hamilton, 1967; Ellis, 1967, 1968; Doenicke et al., 1968), the involuntary muscle movements, hiccup and thrombophlebitis (Clark and Swerdlow, 1966; Lind and Roland, 1969), propanidid remains an extremely valuable drug as an induction agent. In fact it has been described as a safer agent than the barbiturates in some instances, since its quinidine-
like action on the cardiac conductive tissue has a protective anti-arrhythmic action on the heart (Johnstone and Barron, 1968).

Since its introduction into clinical practice, propanidid has been used extensively, especially for out-patient anaesthetics, and in South Africa where porphyric patients are encountered (Howells et al., 1964; Dundee and Clarke, 1964; Goldman and Kennedy, 1964; Swerdlow, 1965; Russell, 1969). Recently, reports of unusual reactions to the drug have appeared in the medical press (Zindler, 1965; Radnay, 1965; Kay, 1969). Russell (1969) reports a case of anaphylactic reaction to a mixture of propanidid and cyclizine, in which cyclizine was shown to be the drug responsible. In the cases reported by Kay (1969), and that of Desai (personal communication), atropine had been given immediately beforehand; making it difficult to establish which of the drugs, or perhaps the drug combination, was to blame for the reaction.

In the case described here, no other drug was administered; propanidid must therefore be implicated as the agent responsible for the unusual reaction seen. However, postoperative immunological studies failed to show any evidence of allergy or hypersensitivity to propanidid. The patient had been exposed to propanidid two weeks previously, and it is thus possible that "sensitization" occurred as a result of this. The failure to demonstrate any allergy may not in itself rule out an immunological reaction as the cause, but the clinical features of the case were so bizarre that it did not seem to be the likely explanation. Drug idiosyncrasies and hypersensitivity reactions, usually associated with the release of histamine, and occurring quite independently of any allergic mechanism, has been described with other drugs (Smith, 1957).

Zindler (1965) reports one case, and mentions two others that had been reported earlier (Zindler, 1964). One had an exanthematous reaction only; the second (reported by Beck) reacted with generalized exanthema and an unrecordable blood pressure; the third case reacted with severe hypotension. The second and third cases were receiving propanidid for the second time—three weeks after a previous uneventful anaesthetic with the same drug. In two cases it is not stated whether atropine was given beforehand, but the third case definitely did not receive atropine.

Radnay (1965) reports a similar case of widespread flushing above the level of the heart, and a fall in blood pressure to an unrecordable level. This case had never received propanidid before; there is no mention of whether atropine had been given.

Desai (personal communication) experienced a similar reaction in a child; widespread flushing and an unrecordable blood pressure, in a case that had previously undergone an uneventful anaesthetic with propanidid two weeks earlier. Atropine had been given immediately beforehand in this case.

Kay (1969) reports two cases, both of whom were given atropine immediately before giving the propanidid, but only one of which had received an earlier exposure to propanidid.

Thus, including the present case, there have so far been eight reported cases of similar untoward reactions to propanidid. Five had received an earlier uneventful exposure to the drug, three had not been previously exposed. Besides the present case, at least one had not received atropine with or before propanidid. The surgical condition of the patients is not known in four, but in the latest four cases they were all toxic children, having operations for the evacuation of pus.

One of the striking observations in the present case, not reported elsewhere, concerns the sudden onset of severe abdominal pain occurring before any of the other changes.

Although no direct evidence of histamine release could be detected in the present case, this would seem to be the most likely explanation for the phenomenon. It remains a puzzle, however, as to why a similar reaction did not occur at the first administration. Had the child not received a previous dose of propanidid, with no untoward effects, then the reaction observed would clearly have been ascribed as due to true drug idiosyncrasy and massive histamine release. Perhaps, as has been shown to occur with thiopentone (Carrie and Buchanan, 1967), propanidid can act as a hapten, combining with body protein to stimulate antibody production; then when challenged with propanidid at some later date, a hypersensitivity reaction can occur. But this does not explain the occurrence of similar severe reactions in patients receiving propanidid for the first time. Whatever
the mechanism in this and the other similar cases, it is strange that it has only been seen so far in toxic children. The pattern of plasma proteins and cholinesterase levels do change in this type of patient, and perhaps it is because of such changes that the grossly abnormal reactions occur.

ACKNOWLEDGEMENT

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REFERENCES


ARRET CARDIAQUE APRES INDUCTION PAR PROPANIDID: DESCRIPTION D'UN CAS

SOMMAIRE

L'auteur décrit une sévère réaction, consécutive à l'emploi de propanidid pour induction d'anesthésie chez un garçon intoxiqué. Il rapporte la succession des événements, culminant dans l'arrêt cardiaque clinique, la resuscitation réussie, le rétablissement et l'enquête faite. On presume qu'une libération massive d'histamine est la cause la plus probable des phénomènes observés, mais le mécanisme ne peut pas être expliqué de manière satisfaite.

HERZSTILLSTAND NACH INDUKTION DER NARKOSE MIT PROPANIDID

ZUSAMMENFASSUNG

Der Fall eines toxisch erkrankten kleinen Jungen wird beschrieben, bei dem es nach Anwendung von Propanidid zur Narkose-Induktion zu einer schweren Reaktion kam. Über den Verlauf der Ereignisse, die einen Höhepunkt in dem klinischen Herzstillsatand fanden, die daraufhin mit Erfolg durchgeführte Wiederbelebung, die Genehmigung und die Untersuchungen wird berichtet. Als wahrscheinlichste Ursache der beobachteten Phänomene wird eine massive Histaminfreisetzung angenommen, für die jedoch keine befriedigende Erklärung gegeben werden kann.