D-PENICILLAMINE INDUCED MYASTHENIA GRAVIS

Its Relevance for the Anaesthetist

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Rheumatoid arthritis can be a very mutilating disease and, as a result, the likelihood of patients with rheumatoid arthritis requiring surgery and anaesthesia is increased. D-penicillamine (D-Pen) has been used in the treatment of rheumatoid arthritis and Wilson's disease since the early 1960s. Its true mode of action is unknown, but it appears to modify the immune response. Treatment with D-Pen is associated with many side effects, one of which is the induction of several conditions of which autoantibody production is a feature; for example, systemic lupus erythematosus, pemphigus, Goodpasture's syndrome, polymyositis, autoimmune thyroiditis and myasthenia gravis (Bucknall et al., 1975; Bucknall, 1977; Gordon and Burnside, 1977). A variety of auto-antibodies may be detected following the administration of D-Pen: anti-nuclear factor, anti-striational antibodies and anti-acetylcholine receptor antibodies (Masters et al., 1977; Russel and Lindstrom, 1978; Vincent, Newsom-Davis and Martin, 1978).

It is this last group of antibodies which is of interest to the anaesthetist, as their presence may have a synergistic effect in precipitating prolonged postoperative apnoea when non-depolarizing neuromuscular blocking agents are used as part of the anaesthetic technique (Argor and Mastaglia, 1979).

Finally, it is interesting to note that, although D-penicillamine-induced myasthenia gravis (D-Pen MG) is well known to physicians, a literature survey back to 1960 yielded only one report of postoperative apnoea secondary to D-Pen MG prolonging neuromuscular blockade (Blanloeil et al., 1980).

**SUMMARY**

The case of a 57-year-old woman with rheumatoid arthritis is presented to illustrate the rare occurrence of a myasthenic syndrome induced by D-penicillamine, which led to prolonged (5.25-h) postoperative apnoea necessitating artificial ventilation.

**CASE REPORT**

A 57-year-old woman (60 kg) with a 13-year history of seropositive rheumatoid arthritis had been treated with first and second line drugs. In 1982 she underwent, uneventfully, an elbow replacement, which was carried out under general anaesthesia.

In October 1983 D-Pen was commenced in a dose of 125 mg day\(^{-1}\). In July 1984 the patient underwent an ankle arthroplasty when her medication consisted of D-Pen 375 mg day\(^{-1}\) and ranitidine 150 mg 12-hourly, the latter used to treat duodenal ulceration which had occurred following indomethacin therapy. Nothing untoward was elicited during her preoperative assessment and her muscle power seemed limited only by the rheumatoid arthritis.

**Anaesthetic management**

Premedication with papaveretum 10 mg and hyoscine 0.2 mg was administered 1 h before surgery. Thiopentone 250 mg and papaveretum 10 mg were used at induction and alcuronium 20 mg was administered to facilitate intubation of the trachea (Portex 8.5-mm cuffed tracheal tube) and to provide muscle paralysis. Suxamethonium was not used. IPPV was carried out using a Manley ventilator with a tidal volume of 600 ml and a minute volume of nitrous oxide 5 litre and oxygen 2.5 litre. The maintenance of anaesthesia...
involved further injections of papaveretum 10 mg and droperidol 2.5 mg. Just after induction, cephradine 1 g was given. A 5-mg aliquot of alcuronium was given 2.75 h before antagonism of neuromuscular blockade to ensure absolute relaxation at a particularly delicate stage of the operation. Enflurane 0.6–5 % was used for a short period to stabilize the arterial pressure, but this was withdrawn 45 min before antagonism. The anaesthetic was maintained for 3.75 h and antagonism was attempted with atropine 1.5 mg and neostigmine 3.75 mg, in divided doses. However, adequate spontaneous ventilation could not be established despite the administration of doxapram 50 mg and naloxone 0.2 mg. The patient was, therefore, transferred to the I.C.U. for continued IPPV (modified Brompton Manley ventilator) with an oxygen:air mixture (1:5 litre min⁻¹). Blood-gas analysis at this time showed a pH 7.47, \( P_{O_2} \) 11.34 kPa, \( P_{CO_2} \) 4.21 kPa and a base excess +1.5 mmol litre⁻¹. Light sedation and amnesia were maintained with midazolam 7.5 mg but no further analgesia was required. Communication was possible with the patient, who demonstrated an extremely weak grip in response to commands.

The patient did not “fight the ventilator” nor did she make any respiratory effort for 5.25 h. At this time she began to breathe spontaneously via her tracheal tube. One hour later the trachea was extubated, once the patient was able to produce consistent tidal volumes of 300–400 ml at a respiratory rate of 12 to 15 b.p.m. on 40% oxygen. Blood-gas analysis at this time was pH 7.42, \( P_{O_2} \) 9.98 kPa, \( P_{CO_2} \) 4.32 kPa, and a base excess of +1.4 mmol litre⁻¹.

**The postoperative period**

On the morning of the first day after operation, the patient was found to be alert and well orientated. However, marked ptosis was noted affecting both eyes, particularly the left, which remained closed unless an active effort was made by the patient to open it. She complained of blurred vision and “seeing double”. Severe ophthalmoplegia was elicited, especially in upward and downward gaze. No other symptoms or signs of muscle weakness were apparent.

A day later her rheumatologist made a diagnosis of D-Pen-induced myasthenia gravis based on the convincing history of myasthenic symptoms. She had been taking D-Pen for 6 months, and 6 weeks before her operation had noticed that her sight was blurring. Two weeks later she noticed that she was developing double vision and her eyelids were becoming heavier, especially in the evenings. There was no other history of note and she had no relevant family history.

The D-Pen therapy was discontinued 2 days after the surgical procedure; subsequent recovery was rapid and complete.

**DISCUSSION**

More than 30 drugs in current clinical use, other than those used in anaesthesia, may interfere with neuromuscular transmission and potentiate non-depolarizing neuromuscular blocking drugs. Awareness of the existence of such effects is important to the anaesthetist to prevent unnecessary morbidity, or perhaps mortality, in what is an eminently avoidable situation (Argor and Mastaglia, 1979). With respect to this presentation, cephradine has not been reported as an inducer of myasthenic syndromes.

Despite the problem of a myasthenic syndrome developing following D-Pen therapy being well known to physicians (Bucknall et al., 1975; Bucknall, 1977), there is a paucity of reports of postoperative complications associated with D-Pen in the anaesthetic literature, a retrospective review of which, to 1960, yielded one case report of prolonged postoperative apnoea (15 h) as a result of a presumed D-Pen-induced myasthenic syndrome (D-Pen MG) (Blanloeil et al., 1980). This conclusion was arrived at clinically and was supported by the patient's long term recovery after the withdrawal of the D-Pen. In the present case, the patient required 15 h of IPPV.

The reason for this lack of information may be the infrequent incidence of D-Pen-induced myasthenia (1 %); the fact that postoperative apnoea is usually attributed to other agents, for example suxamethonium; or that an insufficient number of acetylcholine receptors are blocked to give significant muscle weakness.

D-pen can give rise to a myasthenic syndrome at any time after the initiation of therapy and with a wide spectrum of doses (0.3–1 g day⁻¹) (Bucknall et al., 1975). Its mechanism of action, in the creation of D-Pen MG, is similar to that underlying spontaneous myasthenia gravis, that is, an immune response whereby auto-antibodies directed at the acetylcholine receptor are produced, with a resultant reduction in end-plate potentials and consequent decrease in muscle
The diagnosis of D-Pen MG is a clinical one. Ophthalmoplegia and diplopia are the earliest manifestations, but dysphagia and dysphonia may also occur. The diagnosis is further supported by challenge with an anti-cholinesterase, which should precipitate a dramatic improvement in symptoms, and serological investigations should show increased titres of anti-acetylcholine receptor antibodies. EMG evidence in D-Pen MG is surprisingly sparse in the literature (Fawcett et al., 1982).

Ninety per cent of patients with D-Pen MG have anti-acetylcholine receptor antibodies and, within an individual, the antibody titre is closely associated with the disease status. Withdrawal of the drug leads, in the majority of patients, to a clear and sustained clinical improvement, suggesting a causal relationship. Furthermore, this clinical recovery is accompanied by a progressive decrease in the anti-acetylcholine receptor antibody titre (Vincent, Newsom-Davis and Martin, 1978; Argor and Mastaglia, 1979). The time for antibody titres to decrease by 50% in one study ranged from 35 to 60 days (Fawcett et al., 1982).

We could not include serological or nerve stimulator results, since the patient was confined in a small peripheral hospital without such facilities; we were reluctant to inflict further trauma and the diagnosis was readily and confidently confirmed by an experienced rheumatologist who sees several such cases each year.

The conclusion to be drawn from our experience is that anaesthetists ought to be aware of this problem, since the preoperative findings can be camouflaged or non-existent, and the diagnosis may become clear only in response to direct questioning.

Surgical treatment of patients with rheumatoid arthritis and on D-Pen usually involves the limbs and, therefore, in the planning of anaesthetic technique more consideration may be given to the use of local anaesthesia. If general anaesthesia is considered necessary, atracurium would be the neuromuscular blocker of choice. The procedure should certainly be carried out in an institution with facilities for postoperative artificial ventilation.

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REFERENCES