THIOPENTONE ANAPHYLAXIS
Case Report
BY
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SUMMARY
A severe anaphylactic response occurred following intravenous injection of thiopentone in a patient who had been taking an oral barbiturate for a long time. The immediate management of the case included airway maintenance and oxygenation, restoration of fluid balance, together with administration of steroids and antihistamines. Postoperative mechanical ventilation of the lungs was continued for 4 hours until the signs of anaphylaxis had subsided. Attention is drawn to some of the factors which may precipitate the reaction, and the evolution of modern views on the mechanisms of anaphylaxis is given.

Many millions of thiopentone injections have been given since it was introduced into clinical practice by Lundy in 1934. However, reports of anaphylactic reactions to the drug are rare.

Hayward and Kiestler (1957) described a patient undergoing dental treatment who showed urticaria and laryngospasm after thiopentone 500 mg.

Kivalo, Wist and Mustakallio (1960) reported the development of urticaria and hypotension and Strunk (1962) described the case of a patient who, despite ten previous anaesthetics in which thiopentone was used, developed a severe anaphylactic reaction on the eleventh occasion.

Currie and associates (1966) described a very similar case who had also received thiopentone on ten previous occasions. In 1964 Dinnick reviewed 600 anaesthetic deaths and emphasized the dangers of the use of thiopentone in hypovolaemic patients, but anaphylaxis was not reported.

The hazards of acquiring sensitivity to sodium thiopentone have been pointed out by Anderton and Hopton (1968). These authors suggest that systemic reactions following oral barbiturates may be a pointer to the possibility of more severe consequences when barbiturates are administered intravenously.

CASE REPORT
A 47-year-old woman was admitted for a diagnostic dilatation and curettage. She had a known allergy to fish and aspirin, both substances causing facial and orbital oedema. She had for 18 months been under the care of the dermatologist for a progressive macular rash of allergic origin, distributed over the lower half of the trunk.

Her daily medication consisted of chlorpheniramine 48 mg in divided doses and chlorpromazine 25 mg three times daily. Because she had a tense excitable personality, she was taking amylobarbitone 30 mg three times daily and sodium amylobarbitone 200 mg at night, with no ill effects. Apart from the rash, physical examination revealed no other abnormalities. Her previous surgical history included an adenotonsillectomy, and an appendicectomy at the age of 15 years.

In view of her severe allergic history but normal response to oral barbiturates it was felt that an intravenous induction with thiopentone followed by nitrous oxide and oxygen (3:1) by facepiece and airway would be safe. Nevertheless it was felt prudent to have available in prepared syringes suxamethonium, hydrocortisone, promethazine and also a cuffed endotracheal tube.

Although not premedicated, she was composed on arrival in the anaesthetic room. Pre-oxygenation was carried out for 5 minutes. Her systolic blood pressure was 145 mm Hg and pulse 75 beats/min. Thiopentone 250 mg in 2½ per cent solution was given via an intravenous infusion of Hartmann solution. A Guedel airway was inserted, and the patient allowed to breathe spontaneously, a mixture of nitrous oxide and oxygen (3:1) with a Magill circuit and a fresh gas flow of 12 l/min.

When the theatre attendants removed the blanket it was noticed that her macules were slowly enlarging and becoming weals. The blush area was flushed deep scarlet, and bronchial wheezing was heard. The inspired oxygen concentration was immediately further increased but in a few seconds laryngeal spasm occurred. She was immediately given suxamethonium 50 mg, rapidly intubated, and the lungs inflated with halothane 1 per cent in oxygen in an attempt to relieve the bronchospasm. The systolic pressure now fell to 60 mm Hg and the heart rate exceeded 120 beats/min. Large amounts of fluid were obviously being lost into the weals. One litre of Hartmann solution was given rapidly. Hydrocortisone 200 mg and promethazine 25 mg were
injected into the intravenous infusion. Five minutes later the bronchospasm had improved and her colour was pink. The systolic pressure rose to 100 mm Hg. In view of the inhalation of halothane it was thought that subcutaneous injection of adrenaline should not be used.

The operation was performed rapidly. At its end the mucous membranes were pink, bronchospasm was absent and the systolic pressure had risen to 100 mm Hg, but the urticaria had spread to become large, confluent, irregularly shaped weals each the size of a hand. There was also marked facial and orbital oedema. A further 200-mg dose of hydrocortisone was given and halothane discontinued.

The patient was transferred to the Intensive Care Unit and pulmonary ventilation controlled by a Bird Mark 7 with humidifier. Alcuronium 20 mg was given intravenously and the inspiratory pressure set at 15 cm H2O which produced a tidal volume of 850 ml. The minute volume was 12 l/min. Hartmann solution was continued at 500 ml every 2 hours and hydrocortisone 100 mg was given intravenously every hour.

A sample of arterial blood showed: pH 7.5, P33.5 mm Hg and standard bicarbonate 27 m.equiv/l. Four hours later the weals and erythema had subsided, leaving only faint pink irregular areas. The systolic pressure was 110 mm Hg and chest was clear on auscultation. Neuromuscular blockade was reversed with atropine 1 mg and neostigmine 5 mg and the patient was extubated. She was now alert and talkative, seeming no worse for her experience. However, she was kept under observation for a further 4 hours before being returned to the ward.

Following this reaction she was investigated fully. Eleven profile biochemical parameters were normal, no cryoglobulins were detected and catecholamine derivatives were excreted in normal amounts.

Passive transfer Prausnitz-Kustner tests and patch tests were not performed because of the danger of hepatitis. Minute intravenous challenging doses were considered but as the aetiological agent of this anaphylactic reaction appeared obvious, and as these tests are hazardous (Carrie and Buchanan, 1967), it was considered that the risk was unjustified in this patient.

DISCUSSION

There is no doubt that the patient had an anaphylactic reaction to thiopentone. The constellation of physical signs suggesting anaphylaxis are: (1) peripheral circulatory failure with profound hypotension and tachycardia; (2) respiratory difficulty with bronchospasm, laryngeal spasm and cyanosis; (3) skin phenomena including rashes, erythema and urticaria.

The case reported here showed these features except that hypotension was not profound and was quickly reversed, and that the patient was never cyanosed because the inspired oxygen concentration was raised quickly.

Anaphylaxis was recognized in the early days of experimental immunology, when it was found that a second injection of an antigen into an animal sometimes had harmful, even fatal results. Richet in 1893 coined the not very apt term “anaphylaxis” because he thought it was the opposite of “prophylaxis”, meaning to be on guard. In anaphylaxis the organism is very much “on guard”. Landsteiner (1945) showed that chemical compounds might combine with tissue protein to produce a substance with antigenic properties. Sir Henry Dale, between 1911 and 1914, had showed that most of the anaphylactic phenomena in guineapigs could be reproduced by injecting them with histamine which caused widespread smooth muscle contraction and dilated leaky capillaries.

Next, in 1953, Riley and West demonstrated the presence of histamine in mast cells and showed that these cells are the chief source of histamine in the tissues. All the evidence points to mast cell disintegration and release of histamine as the basis of the anaphylactic reaction (Smith, 1963). It is now (Ham, 1969) postulated that antibody which is produced in response to the first injection of antigen is adsorbed on to the cells, especially the mast cells. At the second antigenic exposure ("the challenge") there is an antigen/antibody reaction at the mast cell membrane which disrupts the intracellular granules, and releases histamine. Mast cells are not the only cells containing histamine. Blood platelets do also. The mast cells of other animal species contain serotonin (5-hydroxytryptamine) which acts rather like histamine. This substance has been found in human argentaffine cells of the gastrointestinal tract. Other compounds implicated in the anaphylactic reaction are the slow-release substance A and bradykinins.

The species variation in the anaphylactic response, and variations of response within the species, probably reflect different patterns of release or sensitivity.

Suggestions and management.

Anaphylaxis may occur without warning, but the possibility might be suspected in patients in whom a history of allergy or asthma is obtained. Cutaneous or generalized reactions following ingestion of barbiturate tablets might be noted, as in the case reported by Anderton and Hopton (1968). The present report, however, shows that otherwise satisfactory oral barbiturate medication is not always a safe indication that an intra-
venous barbiturate will be tolerated. Multiple barbiturate inductions in the past should signal caution. Obviously the possibility of anaphylaxis cannot be foreseen in every case but if the patient has an allergic history the following regimen is suggested.

1. Pre-oxygenation for 5 minutes to ameliorate any respiratory difficulties.
2. Establish an intravenous infusion in case large volumes of fluid are necessary to correct hypotension due to fluid losses through "leaky capillaries" (Dale and Laidlaw, 1919).
3. Have ready: (a) hydrocortisone 200 mg, (b) suxamethonium 100 mg, (c) promethazine 25 mg, (d) adrenaline 1:1000 0.5 ml.
4. A cuffed endotracheal tube of appropriate size.

The rarity of anaphylactic reaction to sodium thiopentone would not justify the use of the newer intravenous induction agents for all the many patients who have a history of allergy, because the responses to these agents in the hypersensitive patient are not known.

If patients do react in this way they should be informed, and advised to wear a "Medic Alert" warning, stating that intravenous barbiturates are dangerous because of the risk of anaphylaxis.

ACKNOWLEDGEMENTS

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REFERENCES


A PROPOS D'UN CAS D'ANAPHYLAXIE AU THIOPENTONE

SOMMAIRE

Une grave réaction anaphylactique est survenue à la suite de l'injection intraveineuse de thiopentone chez un malade ayant absorbé un barbiturique par voie orale, pendant une durée prolongée. Le traitement instauré d'urgence dans ce cas, visait à maintenir les voies respiratoires libres et comportait une oxygénothérapie, une restauration du bilan hydrique, conjointement à l'administration de cortico-stéroïdes et d'antihistaminiques. La mise en œuvre d'une ventilation pulmonaire mécanique post-opératoire a été poursuivie pendant 4 heures, jusqu'à disparition des signes d'anaphylaxie. L'attention est attirée sur certains facteurs susceptibles de précipiter ce type de réaction. Il est fait état de l'évolution des conceptions modernes en matière de mécanismes de l'anaphylaxie.

ANAPHYLAXIE NACH THIOPENTON: EIN FALLBERICHT

ZUSAMMENFASSUNG


ANAFILAXIS POR TIOPIENTONA: COMUNICACIÓN DE UN CASO

RESUMEN

Ocurrió una intensa respuesta anafiláctica después de la inyección intravenosa de tiopentona en un paciente que había estado tomando un barbitúrico oral durante mucho tiempo. El cuidado inmediato de este caso consistió en mantener abierta la vía aérea y oxigenación, restauración del equilibrio líquido, y administración de esteroides y antihistamínicos. La ventilación mecánica postoperatoria de los pulmones fue continuada durante 4 horas hasta desaparecer los signos de anafilaxia. Son señalados algunos de los factores que pueden precipitar la reacción y se revisa la evolución de las opiniones modernas sobre los mecanismos de anafilaxia.
SOCILITY FOR DRUG RESEARCH

Some Recent Developments in Anaesthetic and Neuromuscular Blocking Drugs

Symposium to be held at the Rooms of the Pharmaceutical Society, 17 Bloomsbury Square, London W.C.1, on Wednesday, February 23, 1972. Chairman: Dr D. Jack

10 a.m.
Anaesthetic and Neuromuscular Blocking Drugs

Professor J. P. Payne, M.B., F.F.A.R.C.S., Royal College of Surgeons of England

Revision of the Structures of (+) - Tubocurarine Chloride and (+) - Chondocurine.

Pharmacology of Neuromuscular Blocking Drugs

Professor Eleanor Zaimis, M.D., M.R.C.P., Royal Free Hospital School of Medicine

Evaluation of Neuromuscular Blocking Agents in Experimental Animals
R. Hughes, B.Sc., M.Sc., Ph.D., The Wellcome Foundation Ltd

Pharmacology of AH 8165
D. Jack, Ph.D., Allen and Hanburys Ltd

Neuromuscular Blocking Actions of Aminosteroids
W. R. Buckett, Ph.D., and D. S. Savage, Ph.D., Organon Laboratories Ltd

2.15 p.m.
The Development of CT 1341—a New Steroidal Anaesthetic
B. Davis, B.Sc., M.I.BIOL., Glaxo Research Ltd

Clinical Pharmacology of Ketamine
Professor J. W. Dundee, M.D., Ph.D., F.F.A.R.C.S., The Queen's University of Belfast

Chemistry, Development and Current Status of Fluorinated Inhalation Anaesthetics
W. G. M. Jones, Ph.D., ICI Pharmaceuticals Ltd

Pertubartions of Membrane Structure by Anaesthetics
J. C. Metcalfe, M.A., Ph.D., University of Cambridge Medical School

Summing-up: Professor J. P. Payne

Coffee will be served before the meeting

All enquiries to the Honorary Secretary, Dr Alma B. Simmonds,
Chelsea College, University of London, Manresa Road, London S.W.3