PROTECTIVE HYPOTHERMIA FOR CANCER CHEMOTHERAPY

BY

H. A. CONDON

Royal National Throat, Nose and Ear Hospital, London, England

SUMMARY

Experience is reported of the use of immersion hypothermia on twenty-one occasions in seventeen patients in whom ethoglucid was injected by the intra-arterial route for the treatment of advanced cancer of the head and neck. The main hazards were found to be arterial hypotension occurring during the procedure and postoperative regional oedema leading to respiratory obstruction for which tracheostomy was required on eight occasions. The fall in white blood cell count was appreciably less than that reported after injection of comparable doses at normal temperature. The relief of pain after perfusion was marked.

The treatment of cancer by drugs has become well established in the last twenty years. In this hospital, the practice of intra-arterial perfusion, using ethoglucid, for advanced head and neck cancer has been developed (Harrison and Tucker, 1964) and the associated anaesthetic problems have been described (Condon, 1963).

Ethoglucid (Epodyl, ICI) is a short-acting alkylating agent which chemically is a bis-epoxide. Its metabolic half-life is 8–10 minutes, it being rapidly inactivated by the liver. However, as with other cytotoxic drugs, ethoglucid is not tumour specific and affects all dividing cells, the most important of these being the bone marrow. It is the bone marrow depression following treatment that limits the amount of drug which may safely be administered.

Pioneer experimental work was undertaken by Shingleton and Smith (1961). Dogs under pentobarbitone anaesthesia were subjected to whole-body hypothermia by immersion to 31–33°C, a second group remaining as controls at 37°C. Intravenous nitrogen mustard was administered to both groups, bone marrow and blood count studies being performed beforehand and for some days afterwards; 72 per cent of the control group died but all the hypothermic group survived. It was concluded that hypothermia produced a significant protective effect against a lethal injection of nitrogen mustard in dogs. Those dogs not protected by hypothermia developed a more marked leucopenia with bone marrow hypoplasia.

In this paper, our experiences using protective hypothermia for cancer chemotherapy are recorded. The patients were all suffering from advanced head and neck cancer. Each had been subjected to radical surgery and/or radiotherapy with failure to control the disease.

METHOD

After premedication with pethidine 50 mg and atropine 0.6 mg anaesthesia is induced with methohexitone 50–75 mg. Suxamethonium 50 mg is then injected and auffed endotracheal tube inserted. This is followed by either nitrous oxide, oxygen and halothane in a semiclosed system with spontaneous respiration or tubocurarine for muscle relaxation, an inhalation agent to promote peripheral vasodilatation and artificial ventilation using a Bleas PulmoFloator.

A Godart Haemotonograph is used to monitor the blood pressure. This is an automatic indirect recorder of the systolic and diastolic pressures. Oscillations in the cuffs are detected by sensing the resulting airflow in and out by thermistors (De Dobbeleer, 1965). The e.c.g. is observed on an oscilloscope. Light Laboratories thermistors are used to record the oesophageal, rectal, nasopharyngeal and bone marrow temperatures.

The patient is placed in a collapsible bath previously clamped to the operating table. After
erection, the bath is filled with iced water at 5–10°C. When the oesophageal temperature reaches 32°C, the bath is emptied, dismantled and the patient dried.

The surgical procedure takes from 60 to 90 minutes. The carotid vessels are exposed in the neck and the branch supplying the tumour area isolated. The remaining branches of the external carotid artery are temporarily occluded. A tracer dye, Sulphan Blue (Disulphine Blue, ICI), is injected to confirm that the arterial supply of the tumour is derived from the selected vessel. This is followed by ethoglucid 100–250 mg/kg, special care being taken to avoid air embolism. The temperature after-drop usually reaches its maximum at this time.

Following surgery, the bath is re-erected and filled with warm water at 40°C. When the oesophageal temperature reaches 35°C, residual curarization is reversed and spontaneous respiration restored. After tracheobronchial suction, the endotracheal tube is removed and the patient transferred to the Intensive Care Unit.

RESULTS
Twenty-one perfusions under hypothermia have been carried out on seventeen patients (table I). There were ten men and seven women and the age range was 31–74. There was one death which took place on the third postoperative day (see later).

Spontaneous respiration with halothane was used for six perfusions. Artificial ventilation was used on fifteen occasions, the anaesthetic being halothane (four cases) and diethyl ether (eleven cases). The average time needed for the temperature to fall to 32°C was 55 minutes, after which there was an after-drop of 2–4°C. Rewarming took an average of 75 minutes.

Hypotension.
This was a cause of particular concern in nine patients, systolic levels as low as 30 mm Hg being recorded. The general pattern was that the level gradually fell as hypothermia proceeded, there being further acute falls when the carotid sinus was manipulated and the ethoglucid administered (fig. 1).

There was one episode of ventricular fibrillation.

Case No. 11.
A male, aged 62, had a history of coronary thrombosis ten years previously, and was suffering from recurrent carcinoma after maxillectomy. The blood pressure was 120/80 mm Hg when cooling was started, the anaesthetic being halothane with spontaneous respiration. At the start of surgery, the pressure was 90/70 mm Hg. Manipulation of the carotid sinus caused a drop to 50/30 mm Hg but the pressure recovered to 100/80 mm Hg. Immediately after perfusion, the systolic pressure was 30 mm Hg. During rewarming, the blood pressure was 60/40 mm Hg rising to 100/80. However, when the oesophageal temperature was 32.5°C, ventricular fibrillation developed. After external cardiac massage, artificial ventilation and the administration of sodium bicarbonate, external defibrillation was successfully performed. The blood pressure was 110/90 mm Hg at the conclusion. The postoperative period was complicated by (i) respiratory obstruction after 2 hours for which tracheostomy was required, (ii) disorientation and restlessness for some days, relieved by oxygen therapy, and (iii) laryngeal inco-ordination leading to recurrent chest infection. There was a gradual improvement and he was discharged home after two months.

Respiratory obstruction.
Acute respiratory obstruction from regional oedema in the immediate postoperative phase required urgent tracheostomy in five patients (table I). Elective tracheostomy at the conclusion of surgery, in anticipation of this complication, was performed on three occasions. This complication usually appeared 2–3 hours after surgery.
### TABLE I

Summary of 17 patients in whom hypothermia was induced on 21 occasions for cancer chemotherapy. Based on a table in Harrison (1967).

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Lesion</th>
<th>Ether (E) or halothane (H)</th>
<th>Spontaneous (S) or artificial (A) ventilation</th>
<th>Added CO₂</th>
<th>Lowest oesophageal temp. (°C)</th>
<th>Ethoglucid (mg/kg)</th>
<th>White cell count (cu. mm)</th>
<th>Tracheostomy</th>
<th>Elective</th>
<th>Urgent</th>
<th>Pain relief</th>
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<td>S</td>
<td>—</td>
<td>29.5</td>
<td>120</td>
<td>Died (3rd day)</td>
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<td>—</td>
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<td>29.0</td>
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<td>4200</td>
<td>12</td>
<td>Yes</td>
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<td>29.0</td>
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<td>2350</td>
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<td>—</td>
<td>—</td>
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<td>28.9</td>
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<td>9350</td>
<td>8300</td>
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<td>—</td>
<td>—</td>
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<td>—</td>
<td>27.8</td>
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<td>29.0</td>
<td>150</td>
<td>8490</td>
<td>No drop</td>
<td>—</td>
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<td>7300</td>
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Case No. 1.

A male, aged 31, developed dyspnoea 20 hours after perfusion for carcinoma of the nasopharynx. As he was laid flat on the operating table immediately prior to tracheostomy under local analgesia, cardiac arrest occurred. External cardiac massage and artificial ventilation produced an initial recovery and the operation was carried out. However, irreversible hypotension now existed and death took place on the third post-operative day.

Haematology.

The pre-perfusion white blood count, the lowest count following perfusion, and the day on which this maximum depression occurred, are shown in table I.

One patient had been previously perfused at normal temperature. A comparison of the subsequent blood changes is shown in figure 2. Infection in the neoplasm caused a marked leucocytosis on one occasion.

Skin colour.

The tracer dye, Sulphan Blue, is distributed throughout the body. This makes assessment of the patient's true colour impossible. Excretion of the dye by the kidneys takes up to 36 hours.

Discussion

Apart from being time-consuming, this method of conventional surface cooling proved to be simple and reliable. Shivering was completely abolished. Although this procedure may be carried out with the patient breathing spontaneously, the adequacy of the tidal exchange is problematical and artificial ventilation is now preferred.

Taking into account the nature of the disease, it was considered that to provide maximum protection, hypothermia to an oesophageal temperature of 28–30°C was reasonable. Ventricular fibrillation is unlikely at these levels unless the heart is directly handled.

Hypotension.

Many factors are at work to produce the degree of hypotension which has been recorded in this series:

1. Hypothermia itself produces bradycardia and a reduction of the cardiac output.
2. Halothane acts in four ways: sympathetic block produces vasodilatation; there is central vasomotor depression, direct myocardial depression, and depression of the smooth muscle of the blood vessels.
3. Passive hyperventilation raises the mean intrathoracic pressure, causing the venous return to be reduced.
4. The carotid sinus reflex: pressure on the sinus externally causes bradycardia and hypotension.
5. The cytotoxic drug; ethoglucid is known to produce a fall in blood pressure.
6. Movement—as on drying the patient.

Consideration of these factors indicates measures which were adopted to diminish or prevent hypotension:

1. The substitution of ether for halothane as the agent to promote peripheral vasodilatation and thus speed heat exchange.
(2) The use of negative pressure during the expiratory phase of ventilation will result in a lower mean intrathoracic pressure.

(3) The administration of 5 per cent carbon dioxide will give a normal arterial PaCO, Brady-cardia is less pronounced; arrhythmias are less frequent; the blood pressure is better maintained and electrical defibrillation is easier. Generally, the improved tissue circulation and oxygenation counteracts the tendency to circulatory stasis and metabolic acidosis (Broom and Sellick, 1965).

(4) Atropine, in adequate dosage, may be given for bradycardia (Wylie and Churchill-Davidson, 1966).

(5) Vasoconstrictors, such as methylamphetamine, are not contraindicated (Howat, D. D. C., personal communication).

(6) The wall of the carotid sinus can be infiltrated with 1 per cent procaine. However, because of spread of malignant disease in the neck or reaction to previous radiotherapy, this may not technically be possible (Harrison, D. F. N., personal communication).

The episode of ventricular fibrillation was probably precipitated by inadequate coronary perfusion during periods of hypotension. A blood pressure of 100 mm Hg was maintained during cardiac massage and this demonstrated the value of continuous recording. As the patient was dyed, apart from the state of the pupils, there was no other evidence of the efficiency of the massage.

Respiratory obstruction.

Intra-arterial ethoglucid causes regional oedema to develop in the tissues reached by the drug. Where the upper respiratory tract is involved, this oedema may lead to acute respiratory obstruction for which urgent tracheostomy will be required. The clinical picture is complicated by the fact that the skin is dyed. Constant vigilance must therefore be exercised during the first 24 postoperative hours.

Bone marrow depression.

In considering the white blood count, it will be recalled that there is normally considerable day-to-day variation. Therefore, the trend shown by serial counts is more significant than the result of any individual count.

Generally in man, following a dose of ethoglucid of 150–250 mg/kg the white blood count reaches its lowest point 14 (± 2) days after injection, at which time the mean count is 1000 (± 500)/cu.mm. Recovery is complete by the 21st to 35th day. When the intra-arterial dosage was reduced below 100 mg/kg no white count fell below 1000/cu.mm (Harrison and Tucker, 1964). When, as in this series, the perfusion is carried out under hypothermia, the fall in the white count proves to be appreciably less. Alternatively, an otherwise lethal dose can safely be given.

Originally, it was thought that the uptake of cytotoxic drugs was directly related to cell temperature. The value of hypothermia in protecting normal cells was inferred from the increased uptake at raised temperatures (Rochlin et al., 1961). The early clinical work was therefore based on a combination of whole-body hypothermia with regional perfusion at raised temperatures (Shingleton and Parker, 1960; Leone et al., 1962). Such a procedure is not required when using ethoglucid. The anti-tumour effect of this drug is not decreased under hypothermia and its metabolic life is comparable with that at normal temperatures (Harrison, 1967).

It is more likely that the protective effect is explained by the fall in the white blood count during hypothermia, i.e. there will be fewer circulating white cells exposed to the cytotoxic agent. Helmsworth and Cole (1956) found an 80 per cent drop in the white blood count of dogs who were cooled by immersion to 23 °C for 60 minutes. In radioactive isotope studies in dogs, Villalobos and associates (1958) found that the platelets and white cells during hypothermia were not destroyed but were sequestrated in the liver and spleen. The venules of the mesenteric circulation may be similarly involved (Brewin, 1964).

Relief of pain.

Pain relief has been a striking feature of this work and has more than justified the procedure. This relief would appear to be a manifestation of the neurotoxic effect of ethoglucid (Bond and Wolman, 1965). Some damage is done to nerve fibres of all sizes, but the pain-conducting fibres, which are covered by only one layer of plasma membrane, are more likely to receive permanent damage than better-protected fibres.
PROTECTIVE HYPOTHERMIA FOR CANCER CHEMOTHERAPY

General.

Since the early paper of Shingleton and Smith (1961), there have been scattered clinical reports to which reference has already been made. These comment favourably on the value of hypothermia in such therapy.

Hypothermia has been utilized in other work with cytotoxic drugs to protect the tissues from anoxia. Selvin (1965) used hypothermia with regional perfusion employing vascular occluding balloons combined with a thoraco-abdominal tourniquet; liver hypoxia was a particular danger. Similar work was described by Rioux, Durand and Masson (1965). Clifford, Bhardwaj and Whittaker (1965) induced hypothermia to permit clamping of both internal carotid arteries during perfusion. Aortic occlusion to protect the pelvic bone marrow was used simultaneously. Hypothermia did not, however, lessen the incidence of fatal cerebral complications. These were considered to be caused by profound postocclusion hypotension.

In evaluating protective hypothermia for cancer chemotherapy, the natural history of malignant disease of the head and neck must be considered. Unlike lesions of the thorax and abdomen, such as carcinoma of the bronchus or the stomach, where inoperability rapidly leads to death, patients with advanced head and neck cancer may linger in pain for many months before bronchopneumonia, meningitis or haemorrhage provides release. Against this background, any procedure which may alleviate suffering would seem to be well justified.

It is concluded that in the present series hypothermia has provided protection against the toxic effect of an alkylating agent on the bone marrow and its further use for this purpose is recommended.

ACKNOWLEDGEMENTS

I am grateful to Professor D. F. N. Harrison for his encouragement and co-operation, and for access to case records. I am also indebted to Dr. D. D. C. Howat, of St. George's Hospital, for his advice.

REFERENCES


HYPOTHERMIE PROTECTRICE DE LA CHIMIOThERAPIE CANCEREUSE

SOMMAIRE

On rapporte l’expérience de l’emploi d’hypothermie par immersion, appliquée 21 fois chez 17 malades, chez qui ethoglucid avait été injecté par voie intra-arterielle pour traiter un cancer avance de la tête et du cou. Les risques principaux observés étaient hypotension artérielle durant l’intervention et œdème régional post-opératoire causant une obstruction respiratoire qui
HYPOTHERMIE ALS SCHUTZMASSNAHME BEI DER CHEMOTHERAPIE DES CARCINOMS

ZUSAMMENFASSUNG

Es wird über Erfahrungen bei der Anwendung der Immersionshypothermie berichtet, die bei 21 Gelegenheiten an siebzehn Patienten gesammelt wurden, denen zur Behandlung eines fortgeschrittenen Carcinoms im Bereich des Kopfes und des Nackens intraarteriell Ethoglucid verabreicht wurde. Die Hauptgefahr waren, wie sich herausstellte, die arterielle Hypotension, die während der Prozedur auftrat, und nach der Immersion lokale Ödeme, die zum Verschluß der Atemwege führten, so daß in acht Fällen eine Tracheotomie erforderlich war. Der Abfall der Leukozytenwerte war deutlich geringer als der, der nach Injektion einer vergleichbaren Dosis bei normaler Temperatur angegeben wurde. Die Schmerzlinderung nach der Immersion war beträchtlich.

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