Drugs 1960-1970

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Editor: Graeme S.Avery

19 71

S.Karger · Basel · München · Paris · London · New York · Sydney

Originally published by Australasian Drug Information Services Pty. Ltd.
559 Sydney Road, Seaforth, N.S.W. 2092, Australia

Published exclusively by
S. Karger AG, Arnold-Böcklin-Strasse 25, CH–4000 Basel 11 (Switzerland)
in the whole world with the exception of
Australia, New Zealand, North and South America and Japan

National Library Registry No. Aus69-2994
First Edition 1969

Printed by Clark and Matheson Ltd., 101-107 Albert Street, Auckland, New Zealand

FOREWORD

For the past 10 years the medical profession in Australia has been helped in its work by the publication of New Ethicals, and for five years New Ethicals and Medical Progress has been available in New Zealand. To mark this event, Drugs - 1960 to 1970 was sent to all doctors in both countries in September, 1969. This volume contained numerous articles, by authorities in their chosen fields, on the pharmacological actions and the therapeutic application of many products which have become available in the past 10 years.

This "therapeutic explosion" has given to the medical profession many weapons which may be double edged. On the one hand diseases previously regarded as untreatable, and for which symptomatic relief only could be given, can now have their natural history appreciably prolonged, or be actually aborted. On the other hand, the powerful pharmacological actions of many of these drugs have put into the hands of doctors chemical substances the use of which may, in certain circumstances, be fraught with danger. Particularly is this the case in relation to the interactions which may occur, for various reasons, when the metabolism of one drug affects that of another, and the amount of iatrogenic disease uncovered by monitoring systems is probably only a proportion of that which is actually present. For drugs in 1970, unlike in 1870, are not inactive placebos, effective because of other activities of the doctor, but they are agents with effects that can be beneficial when used with wisdom, but, if they are used with inadequate insight into their indications, contra-indications, and hazards, great harm can result.

The publishers are therefore to be congratulated on their decision to reprint the articles from Drugs - 1960 to 1970 in book form, so that they can be more readily and permanently available to doctors in Australia and New Zealand, and also available to doctors elsewhere. Only good can come of this project, and, in the end, it will be the patients attending these doctors who will benefit from the spirits of wisdom so expertly distilled between these pages.

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December, 1969.

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CONTENTS

DRUGS IN ANAESTHETIC PRACTICE

W. H. J. COLE*, M.B., B.S., D.A., F.F.A.R.A.C.S., M.Sc.

Summary: *The last decade has been notable for the large number of valuable drugs of all kinds which have been introduced into anaesthetic practice.*

Halothane is a satisfactory inhalational anaesthetic agent which combines lack of respiratory tract irritation, rapid postoperative recovery and a low incidence of vomiting. Methoxyflurane is a respiratory tract irritant, but it has analgesic properties and the capacity to produce muscular relaxation which exceed those of halothane.

Five valuable intravenous anaesthetic agents have been developed; methohexitone, propanidid, gamma hydroxy sodium butyrate, diazepam and ketamine. Choice can now be exercised in relation to duration of action, respiratory stimulation or depression and circulatory stimulation or depression.

Alcuronium and pancuronium are two competitively blocking muscle relaxants. Both cause an increase in heart rate, but the immediate effect of alcuronium on the blood pressure is to cause a fall, while pancuronium causes an elevation.

Tacrine and hexaflurenium are anticholinesterase drugs capable of potentiating and extending the duration of action of suxamethonium.

New morphine-like analgesic drugs include phenazocine, dextromoramide, phenoperidine, fentanyl, and propoxyphene. These vary in potency, duration of action and in dependence potential. Pentazocine, an analgesic related to nalorphine, does not produce euphoria and like propoxyphene is considered non-dependence producing.

The neuroleptic drug droperidol, when given with an analgesic, usually either fentanyl or phenoperidine, produces a state of neuroleptanalgesia in which the patient is unperturbed by his surroundings and insensitive to discomfort.

New local analgesics are mepivacaine, which has a quick onset of action with a slightly longer duration of effect than lignocaine; bupivacaine which has an even longer duration of action; and prilocaine which has a lower toxicity relative to analgesic potency than comparable drugs.

Felypressin, an octapeptide vasoconstrictor used for infiltration at an operation site, does not cause as much circulatory stimulation as adrenaline and is said not to act adversely on the heart in the presence of halothane.

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Propranolol and other beta-receptor blocking drugs are of value in treating the effects of accidental overdose of adrenaline or noradrenaline, or of excessive endogenous catecholamine production.

Trimeprazine has sedative, anti-emetic and antihistaminic effects intermediate in degree between promethazine and chlorpromazine. Prochlorperazine and thiethylperazine are anti-emetic drugs of considerable value in postoperative vomiting.

Doxapram, although a respiratory stimulant, is not a specific antagonist to any particular drug.

INTRODUCTION

The last decade has been remarkable for the extraordinarily large number of drugs of all types which have been introduced into anaesthetic practice. In considering the history of development of anaesthesia it can be observed that the discovery of new drugs and agents has not proceeded at a uniform rate. From 1840 to 1850 nitrous oxide, ether, chloroform and ethyl chloride were used, but it was over 80 years before any new general anaesthetic agents were added that were to have a permanent place in the practice of anaesthesia. During the years 1930 to 1935 a great increase in knowledge occurred with the introduction of hexobarbitone, thiopentone ('Intraval', 'Pentothal'), cyclopropane, and trichloroethylene ('Trilene'), with the result that anaesthesia became firmly established as a medical specialty. It is of interest that the Association of Anaesthetists of Great Britain and Ireland was founded in 1933, and the Australian Society of Anaesthetists in 1935. Since 1935 new discoveries have appeared at an accelerated rate and it is proposed to discuss those compounds introduced since 1959.

INHALATIONAL ANAESTHETIC AGENTS

HALOTHANE ('Fluothane')

Halothane was the first, and probably the most important inhalational agent to be introduced in this period. It was synthesised by Dr Suckling, in 1956, and tested on animals by Dr Raventes. Clinical trials were carried out by Johnstone (1956) in Manchester, and by Bryce-Smith and O'Brien (1958) at Oxford. Clinical testing in Australia commenced in 1957, but halothane was not available for unrestricted sale till 1959 or 1960.

Halothane has been spectacularly successful since it was introduced with the result that it has become the most widely used "potent" inhalational anaesthetic agent in the world, and the standard by which other agents are judged. The reasons for this extensive usage include the overall satisfactory properties of halothane, the lack of respiratory tract irritation which facilitates induction, the extraordinarily low rate of postoperative vomiting, and the property of non-inflammability.

Initially the matter of vaporisation of halothane proved a problem since none of the existing vaporisers were suitable. Halothane which has a boiling point of 51°C gives rise to a vapour concentration of about 30 per cent by volume at room temperature. As halothane vapour of this strength is dangerous, safe usage necessitated the development of vaporisers which

would deliver accurately known concentrations of vapour, with a maximum concentration which was limited to a strength that could be safely used. Such a vaporiser was made by the Cyprane Company of Great Britain, and marketed under the name of 'Fluotec'. It rapidly became popular and other similar vaporisers have since been made. An alternative type of vaporiser is that described by Professor Lucien Morris as the "Copper Kettle".

When adminstered in a suitable concentration with nitrous oxide and oxygen or oxygen alone, halothane is a quickly acting anaesthetic agent. Excitement during induction is uncommon. Halothane is not a respiratory tract irritant, and does not stimulate mucus secretion or promote bronchospasm. When surgical depth of anaesthesia has been established there is usually some depression of respiration in which tidal volume is reduced, often with an increase in rate of respiration. Blood pressure usually falls to below pre-anaesthetic levels often with a slowing of heart rate. The heart is sensitised to the action of adrenaline and noradrenaline. Muscular relaxation of the extremities is complete, but a loss of tone sufficient for abdominal surgery is attainable only with relatively high concentration of halothane.

When administration is ceased recovery occurs rapidly, unless high concentrations have been used or the administration has been prolonged. Post-operative vomiting, before the return of consciousness is rare. Shivering is apt to occur in the post-operative period, especially if the weather is cold.

In 1963 cases of post-operative jaundice occurred in which halothane was thought to have a causal relation. Subsequent exhaustive studies showed that while post-operative jaundice was a fairly common condition the use of halothane was not associated with an increased incidence. Nevertheless cases have occurred in which the association of liver damage with the inhalation of halothane has strongly suggested the occurrence of a sensitisation as in the case exhaustively reported by Klatskin and Kimberg (1969).

While halothane is usually administered from standard anaesthetic machines with or without carbon dioxide absorption it can also be given with oxygen alone or with air and oxygen from quite simple equipment. Under armed service conditions or in remote parts of the world this possibility can be a definite advantage.

In addition, halothane is easily the best inducing agent yet available for use, either with or without an intravenous anaesthetic agent, before the irritating vapours of ether, trichloroethylene or methoxyflurane. In this respect it supersedes ethyl chloride.

METHOXYFLURANE ('Penthrane')

Methoxyflurane was developed several years after halothane (Artusio *et al.*, 1960). It is a non-inflammable halogenated ethyl, methyl ether, and like all ethers which have been used in anaesthetic practice it is a respiratory tract irritant. This feature combined with the high boiling point of 104.7°C of methoxyflurane and the consequently low vapour concentration tends to make induction of anaesthesia slow, and if the patient has poor lung function with a tendency to cough this period can be quite difficult. Fortunately the problem can be overcome, either by interposing the inhalation of halothane between the injection of an intravenous anaesthetic agent and the