Adverse Response to Intravenous Drugs

J. WATKINS

A. MILFORD WARD

Adverse Response to Intravenous Drugs

J. WATKINS
and
A. MILFORD WARD

Protein Reference Unit
Department of Immunology
Hallamshire Hospital Medical School
Sheffield, England

1978

ACADEMIC PRESS · LONDON
GRUNE & STRATTON · NEW YORK

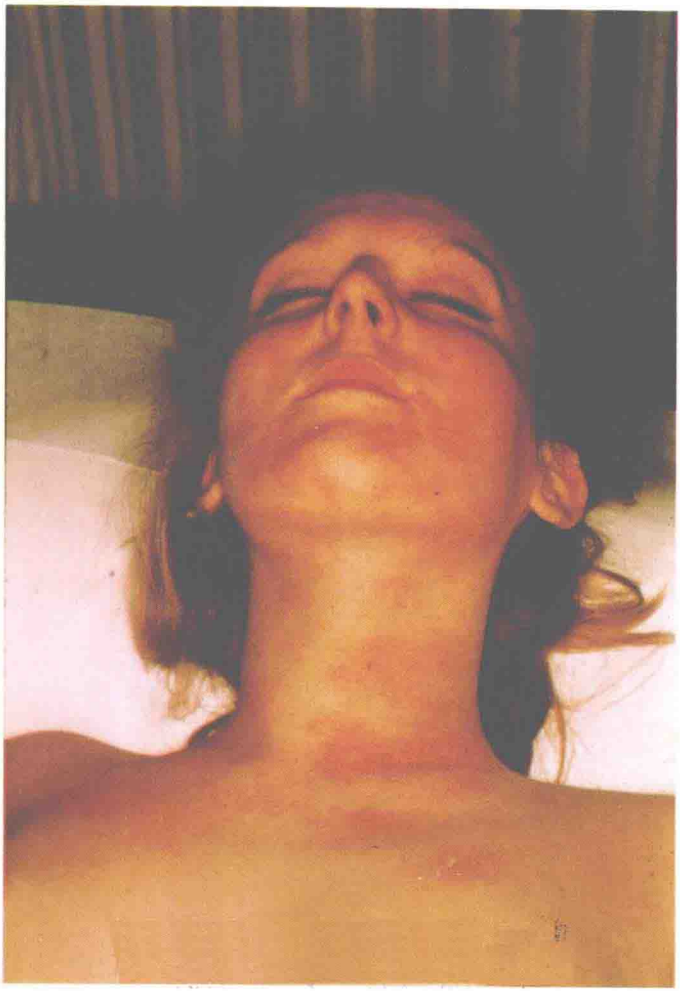
U.K. edition published and distributed by
ACADEMIC PRESS INC. (LONDON) LTD.
24/28 Oval Road
London NW1

United States Edition published and distributed by
GRUNE & STRATTON INC.
111 Fifth Avenue
New York, New York 10003

Library of Congress Catalog Card Number: 77-94302
ISBN (Academic Press): 0 12 737850 2
ISBN (Grune & Stratton): 0 8080 1098 1

Printed in Great Britain by Galliard (Printers) Ltd, Great Yarmouth

Adverse Response to Intravenous Drugs



Generalized urticaria in a volunteer following rapid infusion of oxypolygelatin. No significant increase in plasma histamine level was observed (see Lorenz and Doenicke).

CONTRIBUTORS

ATKINS, D., *PhD, Lecturer in Chemical Pathology, University of Sheffield, Sheffield.*

BENNETT, N.R., *FFARCS, Lecturer, Department of Anaesthetics, University of Sheffield, Sheffield.*

COOKSON, R.F., *PhD, Manager, Anaesthetics and Hospital Products Division, Janssen Pharmaceutical Ltd., Marlow, Bucks.*

CLARKE, R.S.J., *MD, PhD, FFARCS, Reader in Anaesthetics, The Queen's University of Belfast, N.Ireland.*

DAVIES, G.E., *DSc, Senior Scientist, ICI Ltd., Central Toxicology Laboratories, Alderley Park, Macclesfield, Cheshire.*

DOENICKE, A., *Professor, Division of Anaesthesia, Surgery O.P.C., University of Munich, Federal Republic of Germany.*

DUNDEE, J.W., *MD, PhD, FFARCS, Professor of Anaesthetics, The Queen's University of Belfast, Belfast, N.Ireland.*

FEE, J.H., *FFARCS, Research Fellow, Department of Anaesthetics, The Queen's University of Belfast, Belfast, N.Ireland.*

FISHER, M.McD., *FFRACS, Medical Supervisor, Royal North Shore Hospital, St Leonard's 2065, New South Wales, Australia.*

GARRETT, R.T., *MPS, Head of Medical Information, Glaxo Laboratories Ltd., Greenford, Middlesex.*

GLEN, J.B., *BVMS, MRCVS, Biologist, Biology Department, ICI Ltd., Pharmaceutical Division, Alderley Park, Macclesfield, Cheshire.*

HEDIN, H., *PhD, Faculty of Science, University of Uppsala, and Research Biologist, Research Division, Pharmacia AB, Uppsala, Sweden.*

LAMBERT, Susan, *BSc, Product Executive, Anaesthetics Information Service, Janssen Pharmaceutical Ltd., Marlow, Bucks.*

LORENZ, W., *Professor, Division of Experimental Surgery and Pathological Biochemistry, Surgery Clinic of the University, Marburg/Lahn, Federal Republic of Germany.*

MESSMER, K., *MD, Professor of Experimental Surgery, Institute of Surgical Research, University of Munich, Federal Republic of Germany.*

NEWTON, D.J., *MRCP, Travenol Research Fellow, Department of Pharmacology and Therapeutics, University of Sheffield, Sheffield.*

ORR, T.S.C., *PhD, Group Head of Research, Fisons Pharmaceuticals Ltd., Loughborough, Leicestershire.*

RANSOM, P., *BSc, Anaesthetics Liaison Assistant, Janssen Pharmaceutical Ltd., Marlow, Bucks.*

RICHTER, W., *MD, Professor of Immunology, University of Uppsala, and Senior Immunologist, Research Division, Pharmacia AB, Uppsala, Sweden.*

RING, J., *MD, Professor of Immunology, Department of Dermatology, University of Munich, Federal Republic of Germany.*

RUSSELL, R.G.G., *PhD, MD, MRCPath, Professor of Chemical Pathology, University of Sheffield, Sheffield.*
SCARTH, S.C., *BSc, Experimental Officer, Biology Department, ICI Pharmaceutical Ltd., Alderley Park, Macclesfield, Cheshire.*
TAUSSIG, P.E., *PhD, Research Assistant, Department of Anaesthetics, University of Sheffield, Sheffield.*
THOMPSON, A.V., *BSc, Experimental Officer, Central Toxicology Laboratories, ICI Ltd., Alderley Park, Macclesfield, Cheshire.*
THOMSON, D.S., *BSc, Biologist, Pharmacology Division, ICI Ltd., Alderley Park, Macclesfield, Chesire.*
TUCKER, G.T., *BPharm, PhD, Senior Lecturer, Department of Pharmacology and Therapeutics, University of Sheffield, Sheffield.*
UNDOON, S., *PhD, Research Assistant, Department of Immunology, Hallamshire Hospital, Sheffield.*
WARD, A.Milford, *MRCPath, Consultant in Clinical Immunology, Hallamshire Hospital, Sheffield.*
WATKINS, J., *PhD, Principal Scientific Officer, Department of Immunology, Hallamshire Hospital, Sheffield.*
WOODS, H.F., *DPhil, FRCP, Professor of Clinical Pharmacology and Therapeutics, University of Sheffield, Sheffield.*

FOREWORD

When I use a word, it means just what I choose it to mean - neither more nor less. The question is which is to be master - that's all.

Humpty Dumpty - Lewis Carroll

This couplet is an apposite one in the context of this volume, dealing as it does with the subject of adverse drug reactions in a particular situation. Adverse reactions to intravenous drugs may present a wide spectrum of clinical effects from mild facial flushing to cardiac arrest and death; the pharmacokinetics and mechanisms of the reaction are equally diverse; and even the terms used to describe some of the reactions are confused and even misleading on initial inspection, anaphylaxis, anaphylactoid and histaminoid acquiring almost a special meaning in the context of reactions to drugs administered by the intravenous route.

The classic mode of classification of adverse reactions to drugs into overdosage, intolerance, side effects, secondary effects, idiosyncracy and hypersensitivity (Rosenheim and Moulton, 1958) is gradually giving way to the simpler Type A, exaggerated pharmacological action, and Type B, aberrant effects, classification (Rawlins and Thompson, 1977). Most of the reactions and mechanisms discussed in this volume fall into the second of these categories - that of qualitative abnormality in response - the reactions forming a heterogeneous group being neither predictable in relation to the normal pharmacology of the drug, related to dosage, not detectable in the normal toxicological screening during development and manufacture. The incidence of these reactions varies widely from drug to drug, but the mechanisms involved and the pharmakine-

tics of intravenous administration tend to make the morbidity and mortality high. The volume is not intended as a comprehensive treatise on the subject, restricted as it is to anaesthetic agents, muscle relaxants and plasma expanders, but rather as a monograph relating the specific situations and reactions invoked by the route of administration of these agents.

This volume arose out of a Symposium held in the University of Sheffield Medical School in June 1977, at which invited participants discussed the incidence of and mechanisms involved in adverse reactions to intravenous anaesthetic agents and plasma expanders. Various additional chapters have been contributed to the final volume which enlarge both its scope and depth. The volume divides broadly into four sections dealing in turn with clinical aspects and pharmacokinetics, incidence, mechanisms, and management.

The first section consists of three chapters covering the pharmacokinetics of intravenous drug administration and the clinical aspects of adverse reactions in both the general sense and that specifically relating to two intravenous anaesthetic agents.

The second section focuses attention on the incidence of reactions to intravenous anaesthetics and to plasma substitutes. The mechanisms involved in these reactions are discussed in the third section with contributions covering the major biological effector systems, complement, histamine, and prostaglandins, as well as the influence of stress. The section is concluded with reference to responses in animals, with obvious implications to veterinary medicine as well as providing a useful model for the experimental study of reactions in man.

The final section deals with the important question of management of reactions as well as steps that may be taken to limit its effect on future exposure.

The volume concludes with an edited version of the

general discussion which took place at the 1977 Symposium in Sheffield. This is included to air some of the less formalised ideas that were presented at the time; the interval between the Symposium and publication of this volume does not render them any less pertinent although experience in the intervening months has allowed some of these ideas to germinate and even grow to bear fruit.

Sheffield
June 1978

John Watkins
A. Milford Ward

References

Rosenheim, M.L. and Moulton, R. (1958). Sensitivity reactions to drugs - a Symposium. Oxford.

Rawlins, M.D. and Thompson, J.W. (1977). Pathogenesis of adverse drug reactions. in Textbook of Adverse Drug Reactions, Ed. D.M. Davies, Oxford Medical Publications.

ACKNOWLEDGEMENTS

The first Symposium on this topic was held informally in the University of Sheffield Medical School on 30 June 1977. We gratefully acknowledge the support given by Fisons Ltd. (Pharmaceutical Division), Glaxo Laboratories Ltd., Imperial Chemical Industries Ltd. (Pharmaceutical Division) and Janssen Pharmaceutical Ltd., which made the Symposium possible and ultimately led to the publication of this volume. Publication coincides with a second International Symposium on the same topic held in Sheffield in July 1978.

Our thanks are due to Mrs. Judy Sibley of Academic Press for her helpful collaboration during the production of this volume and, of course, to our various contributors. Finally, we wish to thank Miss Margaret Eddell who typed the entire manuscript.

CONTENTS

CONTENTS

PHARMACOKINETIC ASPECTS OF THE INTRAVENOUS BOLUS

G. T. TUCKER

Department of Pharmacology and Therapeutics,
University of Sheffield Medical School,
Hallamshire Hospital, Sheffield S10 2RX

An understanding of mechanisms of adverse responses to intravenous agents is incomplete without an appreciation of factors affecting drug delivery to sites of toxicity. Although the clinician has control over the rate of drug input, once the agent leaves the syringe a complex sequence of events is initiated which he can do little to influence other than sometimes by injection of further compounds. The chambers of the heart and the lung are the first structures to be exposed to the agent, while within the vascular space interactions may occur with both fixed and mobile receptors. Distribution to other tissues, including those ultimately responsible for removal of the agent from the body, is in proportion to their share of the cardiac output.

Injection Rate and the Concentration of the Bolus

If a dose of 100 mg of a drug is rapidly injected into the antecubital vein, what sort of concentrations will be achieved at the threshold of the first capillary bed to be encountered, namely that of the lung?

In order to make some rough calculations we must first suppose that none of the dose diffuses through the venous wall into the subcutaneous space at the site of injection. This phenomenon is a possibility, particularly with highly lipid-soluble drugs, but there appear to be no data on the

subject. However, assume that such temporary drug losses are negligible. Assume also that the volume of blood between the vein and entry into the lung is about 160 ml, comprising 8 ml for cubital fossa to superior vena cava (40 cm length, 0.5 cm diameter), 40 ml for the superior vena cava itself, 90 ml for the right heart and 20 ml for the pulmonary artery and that it takes about 6 seconds to travel the distance (Crawford, 1966). Accordingly, injection of the dose at a constant rate over 10 seconds should result in a slug of drug entering the lung at a concentration of about 375 μg/ml. At times before re-circulation occurs this concentration should decrease in proportion to any increase in injection time. Obviously, if the latter is prolonged beyond the fastest re-circulation time, drug returning from other tissues will begin to add to the input concentration to the lung. Initially, the magnitude of this contribution may oscillate since fractions of the primary bolus delivered to various organs will return at different times. The oscillations soon become negligible, however, as a pseudo distribution equilibrium is approached throughout the body and elimination proceeds.

The Strategic Position of the Lung

Because it receives all of the cardiac output and, therefore, all of an intravenous injection, the lung is in an ideal position for protecting other organs from high drug concentrations in the bolus. This is illustrated in Fig. 1 which shows how the lungs attenuate acute concentrations of lignocaine in the pulmonary artery such that the arterial concentrations supplied to the main target of toxicity, the brain, are much lower. The concentration-time profile in the carotid arteries should be similar to that in the brachial artery.

This "buffering" effect of the lung may be achieved in several ways. Firstly, as in any organ, blood entering the lung during a given time interval will not leave as the same unit at some later time but will be dispersed with

respect to time. Thus, there are a multiplicity of blood transit times. The mean transit time for the lung is about 7 seconds, although the exact value will depend upon ventilation and posture; there is also evidence that the distribution of transit times is skewed and multimodal (Neufeld, 1971). The effect of transit, therefore, is to 'smear out' the incoming bolus such that it has a lower 'warhead' concentration which decreases progressively towards a 'tail' (Crawford, 1966).

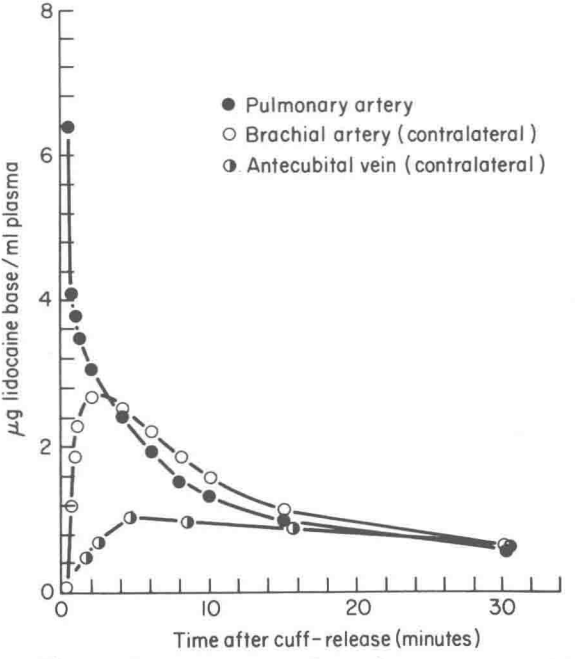


Fig. 1. Plasma lignocaine concentrations in a subject following cuff release after intravenous regional anaesthesia. 3 mg/kg lignocaine HCl 45 min cuff time. Reprinted by permission from Tucker and Boas (1971). *Anaesthesiology*, 34, 538.

If extravascular uptake of drug occurs in the lung its mean transit time will be prolonged over blood transit time, resulting in even greater reductions in drug concentration (Sierler, 1961). In particular, basic lipophilic amine drugs such as lignocaine, propranolol, imipramine and methadone are highly concentrated in the lung (Anderson *et al*, 1974; Dollery and Junod, 1976; Junod, 1972, 1975; Ludden, Schanker and Lanman, 1976). For

example, in isolated perfused rat lungs tissue/medium ratios of up to 17 have been observed with imipramine, with an extraction of 90% of circulating drug (Junod, 1972). The mechanism of uptake of these drugs appears to involve a saturable carrier mediated component, quite separate from the system that scavenges endogenous amines such as 5-hydroxytryptamine and noradrenaline (Junod, 1975). Several theoretical consequences follow from these observations, although their clinical significance is unknown. If uptake is saturable, successive bolus injections should result in more of the dose escaping first-pass removal as drug accumulates in the lung from previous injections. The chances of precipitating systemic drug toxicity may also be increased when two or more basic drugs given sumultaneously compete for lung uptake. Similarly, administration of one drug could provoke the release of an already stored drug or drug metabolite with undesirable consequences.

In addition to binding as a mechanism of drug uptake by the lung, a role of ion-trapping is also indicated. The extravascular pH of the lung may be very low (about 6.7 in the dog) (Effros and Chinard, 1969). Therefore, a large pH gradient between blood and lung tissue will encourage weak bases to be more ionised and, therefore, more concentrated in the lung; the reverse will be true of weak acids such as the barbiturates (Effros, Corbeil and Chinard, 1972). A corollary of this is that acid-base disturbances have a profound effect on lung uptake of partially ionised drugs. The extravascular pH of the lung seems more closely linked to arterial pH than the cellular pH's of other tissues which tend to follow pCO_2 changes. In the lung local alterations in tissue pH due to pCO_2 changes appear to be buffered quite rapidly (Effros, Corbeil and Chinard, 1972).

Apart from transit and uptake, metabolic breakdown of drugs within the lung might also lower exit drug concen-