contains more than 10 mg of iron daily. Blood loss is often a hidden and treacherous condition, and may continue from some unsuspected site when the most obvious sources have been investigated and found apparently normal. Bleeding from the caecum is notoriously likely to escape early detection. Aspirin is a frequent cause of either acute haemorrhage or anaemia from mild chronic loss; it also produces fairly profound and long-standing changes in the haemostatic mechanisms so that mild mucosal breaches may be more apt than normal to bleed. Haemorrhage—either acute or recurrent into serous cavities or into tissues such as the lung—may occur even to the extent of causing jaundice from haemoglobin breakdown. In tropical countries many additional causes have to be remembered; hookworm infestation is the commonest cause of chronic blood loss at present in the world.

OVERT OR OCCULT HAEMOLYSIS

Though some degree of increased red cell destruction is a component of many kinds of anaemia, in haemolytic anaemias it is the predominant or only abnormality, and may be severe. Once again there are many causes—including intrinsic defects of, or injury to, the red cells, or destruction of the cells by antibodies circulating in the blood or coating the cell itself. Intrinsic cell defects may be inherited such as hereditary spherocytosis and the various haemoglobinopathies, or acquired as in paroxysmal nocturnal haemoglobinuria. Autoimmune haemolytic anaemias, usually with a positive direct antiglobulin (Coombs) test, are caused by antibodies with many varying characteristics, and are often though not invariably responsive to treatment with adrenocortical steroids or other immunosuppressive agents. Sometimes these acquired autoimmune haemolytic anaemias arise with apparent spontaneity, but on other occasions they are secondary to diseases such as chronic lymphatic leukaemia or systemic lupus erythematosus.

Various drugs may cause a haemolytic state: alaphamethyldopa

often gives a positive direct antiglobulin test without overt haemolysis, and much more rarely a haemolytic anaemia responsive to steroids. With phenacetin and other drugs, the mechanisms are rather different. Hypersplenism has been mentioned as a cause of haemolysis. Purely mechanical buffeting of red blood cells in damaged blood vessels may be responsible for very obvious haemolysis, as in some forms of arteritis, sometimes in malignant hypertension, and also when heart valves (especially the aortic valve), have been replaced by artificial prostheses.

MIXED MECHANISMS

Though often very obvious and clinically important, the anaemia of many severe pathological processes is still obscure and certainly complex in its causation. This applies to the anaemia of infection or severe chronic inflammation and to that of malignant disease and renal failure. In all of these the red cell survival time is diminished and the capacity of the bone marrow to respond to blood loss or destruction is impaired. In chronic inflammatory diseases such as rheumatoid disease there appears also to be an inability of the marrow to utilize iron properly so that, though the stores are full, the serum iron is low and the red cells hypochromic. In renal and malignant disease the main mechanism, whatever its detail, appears to be an unfavourable balance between red cell destruction and replacement. In renal failure lack of renal erythropoietin may be an important factor.

The more important and common of these processes and their treatment, in their clinical setting, will be considered in the articles that follow in this series.

References

- ¹ Fry, J., in *Profiles of Disease*. Edinburgh and London, Livingstone, 1965.

General Practice Observed

Awareness and Experience of General Practitioners of Selected Drug Interactions

J. C. PETRIE, J. G. R. HOWIE, D. DURNO

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Summary

The awareness of general practitioners of selected adverse drug interactions has been assessed. The drugs studied included adrenergic neurone blockers, warfarin, antidiabetic agents, and monoamine oxidase inhibitors. The findings must

be interpreted with caution but they suggest that there is a clear need to improve the effectiveness of communication of information about adverse drug interactions if unnecessary iatrogenic disease is to be avoided.

Introduction

There is a clear need to ensure that information about clinically important adverse drug interactions is communicated effectively to those doctors who are starting treatment with drugs known to carry such risks. This study aimed to find out whether a group of general practitioners was aware of some of the potential drug interactions involving five groups of drugs—adrenergic neurone blockers, warfarin, antidiabetic agents, monoamine oxidase inhibitors, and sedatives. An attempt was

Department of Therapeutics and Clinical Pharmacology, University of Aberdeen

J. C. PETRIE, M.B., M.R.C.P., Senior Lecturer

Department of General Practice, University of Aberdeen

J. G. R. HOWIE, M.D., Senior Lecturer

D. DURNO, M.D., M.R.C.G.P., Part-time Lecturer

also made to find out whether the doctors had encountered these interactions in general practice.

Method

A 50-item questionnaire with an explanatory letter was sent to all 253 general practitioners in the north east of Scotland region (population 443,000). A letter explained the aims of the study. All drugs were described by approved and proprietary names (where applicable). The form was completed anonymously and a postcard was returned under separate cover to indicate that the questionnaire had been completed. At the end of four weeks doctors who had not replied were sent a reminder (December 1971-January 1972).

Results

The questionnaire was returned by 185 doctors. The principal interactions heard of are set out in the table.

INTERACTIONS INVOLVING ADRENERGIC NEURONE BLOCKING DRUGS

The interaction which had been heard of most often involved the tricyclic antidepressant group; the interaction involving amitriptyline and imipramine was known to 46% of doctors who replied, and those involving trimipramine and nortriptyline to 33% and 30% of doctors respectively. Actual clinical experience of an adverse drug interaction involving this group of antihypertensive drugs was reported by 14% of the doctors who replied.

INTERACTIONS INVOLVING WARFARIN

The least known interactions were the theoretical interaction of warfarin with sulphonamides (familiar to 31% of doctors), with indomethacin (30%), with tetracyclines (21%), with glutethimide (21%), with dichloralphenazone (16%), with mefenamic acid (16%), with ethacrynic acid (8%), and with nalidixic acid (7%). Clinical experience of an adverse drug interaction involving warfarin was reported by 19% of the doctors who replied.

OTHER INTERACTIONS

The awareness and experience of drug interactions involving

chlorpropamide, tolbutamide, insulin, monoamine oxidase inhibitors and sedatives are also shown in the table. Of the 50 drug interactions on the questionnaire the average number which the doctors claimed to have heard of was 17.2. Sixty-six per cent. of the doctors claimed not to have experienced any of the listed drug interactions; 94% of the doctors who returned the questionnaire asked for more information about the interactions.

Discussion

There is obviously a need to improve the effectiveness of the communication of information about adverse drug interactions. The results must of course be interpreted with caution. The questionnaire was completed anonymously and 27% of doctors did not reply. Not all the interactions were of equal clinical importance and some of the practitioners might not have been familiar with different members of an individual drug group or with some of the drug combinations containing a "hidden" substance with a theoretical potential to interact. In addition, the findings are based on the reports by the doctors and cannot be verified because of the design of the study.

ADRENERGIC NEURONE BLOCKING DRUGS

These drugs may contribute to symptoms of depression and nasal congestion. Potential drug interactions^{1,3} with tricyclic antidepressants and sympathomimetic decongestants have been documented in one-third of patients on long-term therapy.⁴ There should be further publicity about these interactions and the issue of warning cards with details of drugs to avoid. This would make doctors and patients more aware of the potentially hazardous pressor responses and loss of control of previously adequately controlled blood pressure which may occur. The real nature of these hazards is apparent as interactions in this category were claimed to have been experienced, and these drugs are widely prescribed. Since several such interactions will not have been recognized because of a lack of awareness of the potential interaction the clinical relevance of this study becomes apparent.

WARFARIN

Theoretical drug interactions⁵ have been noted in one-third of patients on long-term anticoagulant therapy with warfarin.⁴ This is due partly to inefficient transfer of information about the current drug therapy of each individual patient,⁶ but the lack of awareness of the possibility that an adverse interaction

TABLE 1—Principal Interactions Heard of and Experienced by 185 Practitioners Completing Questionnaire

Effect of Interaction	Drug	Prescribed with	% Heard of:	% Actually experienced:
Loss of antihypertensive effect	Adrenergic neurone blockers (bethanidine, debrisoquine, or guanethidine)	Tricyclic antidepressants (4 preparations) Amphetamine Sympathomimetic agents (10 combined preparations)*	30-46 31	13 3
Increased or reduced anticoagulant effect	Warfarin	Salicylates Barbiturates - individual (2) - in combined preparation (6) Phenylbutazone Clofibrate Others (9)	12-32 54 48 26-46 43 37 (see text)	9 8 8 9 4 4
An increase in hypoglycaemic effect	Sulphonylureas (chlorpropamide, tolbutamide)	Phenylbutazone Salicylates Sulphaphenazole	31 38 21	1 2 0
Adverse reactions	Insulin Monoamine oxidase inhibitor	Propranolol Antidepressants Phenothiazines Antihypertensive agents Barbiturates Decongestants Others (foods and drinks - 3) are prescribed	28 78 64 63 52 45 43-71 51	3 1 1 3 0 1 0 5
Altered rates of drug metabolism if	Sedative drugs (3) (except nitrazepam)			

*containing phenylpropanolamine, phenylephrine, or ephedrine.

may be initiated is equally important. Though some of the drug interactions involving warfarin were apparently widely known to the doctors taking part in this study the awareness of the less well publicized interactions fell steeply. Probably some of these interactions are of minor clinical importance and the risks should not be overstressed until the relative importance of each interaction has been evaluated. It is of interest that half the practitioners were aware of the adverse interaction between salicylates and warfarin though this usually occurs only at doses of salicylates (> 3 g) well beyond the doses usually prescribed or taken as selfmedication. On the other hand, the clinically-important interaction involving clofibrate was known to only one doctor in three.

ANTIDIABETIC AGENTS

The low degree of awareness of potential interactions⁷ involving these drugs suggests that, though the occurrence of drug interactions occurring in patients on these agents is potentially high, they may be clinically less significant.

MONOAMINE OXIDASE INHIBITOR DRUGS

The doctors who replied were most aware of the adverse interactions involving this group of drugs. Indeed, five of the six best known interactions involved this group. This high degree of awareness reflects the publicity that these interactions⁸ have received. Hence the risk of the initiation of unintentional drug interaction may be least with this group of drugs though the clinical effects of the interactions may be the most important. The low reporting of clinical interactions may reflect the effectiveness of education in this area.

COMBINED PREPARATIONS

In the present study the awareness of the interacting sub-

stance, such as barbiturate or sympathomimetic agents, was reduced when the substance was "hidden" in the fixed-dose proprietary preparations. This emphasizes the need for doctors to be aware of the components of the combined preparations that they use.

The findings relating to interactions actually experienced have the limitations common to all voluntary reporting systems. If a doctor is not aware of the existence of an adverse drug interaction he will be unlikely to recognize and report it. Nevertheless, the information in this study about the reactions experienced is of some interest in assessing the relative importance that the practitioners attach to the clinical problem of drug interactions.

Doctors clearly wish to have relevant information about clinically important drug interactions but the advice must be practical and authoritative. The distribution of extensive information about drugs that doctors hardly ever prescribe reduces the effectiveness of important information. Since the completion of this study tables of several clinically important adverse drug interactions have been circulated to all the practitioners in the region. As an additional measure warning labels, with detailed information about drugs that interact, are being designed to attach to the hospital and general practice records of patients on specific drugs.

We wish to thank the practitioners of the north east of Scotland for their co-operation with this study.

References

- ¹ Mitchell, J. R., Cavanaugh, J. H., Arias, L., and Oates, J. A., *Journal of Clinical Investigation*, 1970, **49**, 1596.
- ² Leishman, A. W. D., Matthews, H. L., and Smith, A. J., *Lancet*, 1963, **1**, 112.
- ³ Gulati, O. D., Dave, B. T., Gokhale, S. D., and Shah, K. M., *Clinical Pharmacology and Therapeutics*, 1966, **7**, 510.
- ⁴ Starr, K. J., and Petrie, J. C., *British Medical Journal*, 1972, **4**, 133.
- ⁵ *British Medical Journal*, 1971, **4**, 128.
- ⁶ Beveridge, T., and Petrie, J. C., *British Medical Journal*, 1972, **2**, 37.
- ⁷ Martin, E. W. in *Hazards of Medication*. Philadelphia, Lippincott, 1971.
- ⁸ Sjöqvist, F., *Proceedings of the Royal Society of Medicine*, 1965, **58**, 967.

Occasional Survey

Acute Terminal Ileitis and Yersinia Infection

J. F. GURRY

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Summary

Acute terminal ileitis was for many years thought to be due only to Crohn's disease, though most patients found at laparotomy to have this condition did not progress to the chronic form of Crohn's disease. A case of acute terminal ileitis due to Yersinia pseudotuberculosis is presented here to draw attention to another, perhaps predominant, cause of this condition.

Introduction

Though *Yersinia pseudotuberculosis* has been known to be a cause of terminal ileitis and mesenteric lymphadenitis for some 20 years¹⁻³ yersinia ileitis is still rarely recognized. Only 20 or so such cases were diagnosed in the United Kingdom during 1959-72⁴ and none have been reported in the British literature since then. The condition may be misdiagnosed as acute Crohn's disease, and since the prognosis and treatment of the two conditions differ it is important that the differentiation be made.

Case Report

A 12-year-old boy was admitted to this hospital on 2 March 1973 with a two-day history of feeling unwell and pain in the right iliac fossa. He had vomited twice before admission and had not opened his

Professorial Surgical Unit, St. George's Hospital Medical School, London SW17 0QT
J. F. GURRY, F.R.C.S., F.R.A.C.S., Lecturer