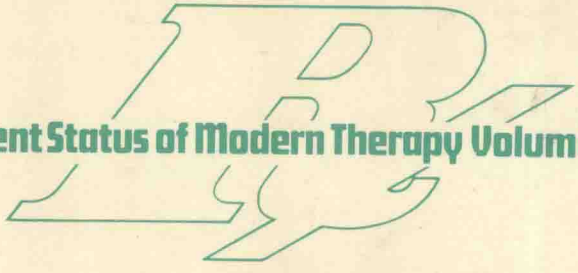

The Treatment of Medical Problems in the Elderly

Edited by M.J. Denham

CURRENT STATUS OF MODERN THERAPY: VOLUME 3

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Consultant Editor's Note

CURRENT STATUS OF MODERN THERAPY

The *Current Status of Modern Therapy* is a major series from MTP Press with the purpose of providing a definitive view of modern therapeutic practice in those areas of clinical medicine in which important changes are occurring. The series consists of monographs specially commissioned under the individual editorship of internationally recognized experts in their fields. Their selection of a panel of contributors from many countries ensures an international perspective on developments in therapy.

The series aims to review the growth areas of clinical pharmacology and therapeutics in a systematic way. It is a continuing series in which the same subject areas will be covered by revised editions as advances make this desirable.

As the diseases of youth and middle age are cured, so the proportion of elderly people in the population of industrially developed countries rises. This means that more general and medical resources must be devoted to geriatric care.

Hence *The Treatment of Medical Problems in the Elderly*, Volume 3 in the *Current Status of Modern Therapy* series, edited by Dr Denham, comes at an opportune time. In this book, with a galaxy of talent among the authors, he shows that we are moving out of the period of care of the elderly as just an art, to care of the elderly as a science and an art. Previously geriatric medicine was the Cinderella of the medical specialities. Now it is coming into its own as studies of the type described so well in this book show how we can add not only years to the life but more importantly life to the years.

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Series Editor

Preface

It has been said that geriatric medicine is the last stronghold of those physicians whose interest is general medicine. Although some diseases are rarely seen, a wide range of illnesses do occur, and indeed the non-specific presentation of disease in the elderly, with the associated problems of diagnosis, is one of the attractions of the specialty. It is increasingly recognized that medical care of the elderly requires special expertise and the fact that the patient is old is not, of itself, a reason for diagnostic or therapeutic lassitude or nihilism. Elderly people deserve and should receive the best medical care available, given with discernment, enthusiasm and kindness.

The extensive nature of illness in the elderly means that the physician in geriatric medicine has to keep up to date with advances in knowledge, management and therapeutics in a wide range of subjects, not only in his own speciality, but also in other spheres which have implications for the treatment of the older person. The selected topics in this book aim to give informed comment in areas where there have been developments, controversy, or where the geriatrician may not be an expert, but where correct management and treatment is essential. It is hoped that the subject matter will appeal not only to physicians in geriatric medicine, but also to physicians and surgeons who are increasingly likely to have to treat elderly patients due to the rising proportion of older people in the population.

M. J. DENHAM

Contents

1

Clinical pharmacology and the elderly patient

K. O'Malley, M. Laher, B. Cusack and J. G. Kelly

INTRODUCTION

The elderly patient differs from his younger counterpart in many important ways, not least with respect to drug therapy. As an almost inevitable part of ageing, the elderly suffer from many degenerate disorders and in addition are susceptible to other diseases. The resultant signs and symptoms not infrequently elicit the 'prescription reflex' by which the doctor attempts alleviation of all or most problems. The large scale of prescribing puts the elderly at increased risk of developing adverse drug reactions. The elderly patient may exhibit altered pharmacokinetics (absorption, distribution, metabolism and excretion of drugs) and pharmacodynamics (the time-course and magnitude of drug effect). Matters are complicated further by the attitude of the elderly to medical intervention. In addition, infirmities such as confusion, poor sight, forgetfulness and failure to comprehend instructions militate against the patients adhering to a therapeutic regimen, both pharmacological and otherwise.

In the present chapter we shall discuss adverse drug reactions, compliance, pharmacokinetics and pharmacodynamics as they pertain to the elderly patient. The clinical importance of these and possible means for taking them into account will be examined.

ADVERSE DRUG REACTIONS

Adverse drug reactions are difficult to monitor and the reported incidence varies from 0·4%[1] to 35% of patients[2]. Papers which

report very low incidences of adverse reactions have been based on retrospective studies which rely on reactions being reported to the investigators or on reports being entered in patients' notes. Studies which show higher incidences have been prospective studies where investigators have actively sought adverse reactions. Retrospective studies probably underestimate the incidence of adverse reactions as only serious or life-threatening reactions are included. Prospective studies on the other hand include many trivial reactions and because of observer bias non-iatrogenic disease or placebo effects may be mistaken for adverse drug reactions[3]. Many studies contain numbers too small to allow assessment of age as a factor in the causation of adverse drug reactions.

Reactions requiring hospital admission

In some well-known studies the incidence of adverse reactions leading to hospital admission has been prospectively examined. Hurwitz[4] examined 1268 patients admitted to hosptial and found that 2·1% were admitted because of adverse reactions to drugs taken for therapeutic reasons. Although there was some indication of a correlation between reactions and age, she did not give detailed figures and when allowance is made for the fact that admission to hospital for *all* reasons was correlated with increasing age the data relating age to incidence of adverse reactions becomes less convincing. Caranasos *et al.*[5] examined 6063 admissions to hospital over 3 years and found that 2·9% of admissions were due to drug-induced illness. Results from this study, adjusted to show the incidence of adverse reactions as a percentage of all admissions in the relevant age group, are shown in Table 1. A modest increase in this incidence may be seen from 61–80 years.

Table 1 Hospital admissions due to adverse drug reactions (modified from Caranasos *et al.*[5])

Age range (years)	*All admissions* (no.)	*Adverse reactions* (%)
11–20	394	2·8
21–30	782	2·4
31–40	746	2·7
41–50	1006	2·1
51–60	1225	2·7
61–70	1213	3·6
71–80	546	4·8
81–90	139	2·2
91–100	12	0

In a recent study[6] 1998 patients who were admitted to geriatric departments in the United Kingdom were assessed for adverse reactions. Of these, 12.4% were judged to have had adverse reactions. Hospital admission was due solely to adverse reactions in 7·7% of cases. Hypotensive agents and antiparkinsonian drugs were most likely to produce adverse effects.

Reactions occurring in hospital

Most investigators report a 10–12% incidence of adverse drug reactions in hospital in-patients. In most cases there seems to be an increased incidence with advancing age. Hurwitz[7] showed a significant correlation between increasing age and adverse drug reactions from a total of 1160. The incidence in those aged 60–69 was twice that observed in those aged 30–39. Patients aged 70–79 had four times the incidence of those aged 30–39 (Table 2).

Table 2 Adverse drug reactions observed in hospital (from Hurwitz[7])

Age range (years)	*No. given drugs*	*% with adverse reactions*
10–19	64	3·1
20–29	100	3·0
30–39	122	5·7
40–49	159	7·5
50–59	222	8·1
60–69	252	10.7
70–79	178	21·3
80–89	59	18·6
90–99	4	0

In a similar study Klein *et al.*[8] indicated that there was an increased incidence of adverse reactions with age and although no detailed statistical analysis was attempted the results suggest that the incidence of adverse reactions in those aged more than 60 years was about three times that in patients aged less than 60 years. Part of this difference was due to a large sex-linked component whereby women aged more than 60 years had a much higher incidence of relatively mild adverse reactions.

Siedl *et al.*[9] also showed an increased incidence of adverse reactions with age although the difference between young and old was not as marked as in some other studies. Again elderly women accounted for a large proportion of mild or moderate adverse reactions (mostly intestinal side-effects).

Problems in assessing the incidence of adverse reactions

Most studies published show some increased incidence of adverse drug reactions with increasing age, but in many cases good statistical analysis is lacking. It is sometimes difficult to assess genuine age-related differences in the incidence of reactions since hospital admissions for *many* causes contain a disproportionately large number of elderly people. When defined populations are monitored continuously little attention is paid to the fact that the population is constantly decreasing since patients are leaving at intervals and therefore, bias in the population readily creeps in. Where studies are prospective, investigators who examine patients may find it difficult to retain objectivity.

While there is little dispute that older patients tend to have a moderately higher incidence of adverse drug reactions more work needs to be done in the field of assessing the clinical significance of these reactions. In particular the relative incidence of serious or life-threatening adverse reactions in the young and old requires further investigations since even in fairly large studies, numbers of these are too small to allow adequate correlation with age. We suspect that the higher reported incidence of adverse reactions in the elderly may in part at least reflect greater drug consumption in this group.

COMPLIANCE

No matter how carefully drugs are prescribed, patients will not derive full benefit from their medication unless they adhere to an appropriately prescribed regimen. A substantial literature has accumulated concerning the magnitude of non-compliance and although it is extremely difficult to assess compliance accurately, results indicated that non-compliance is a major factor in determining a response to a therapeutic regimen requiring self-administration[10]. In a review of published studies Blackwell[11] suggested that 25%–50% of patients did not take their medication at all. Sackett[12] summarized the results of 14 studies on compliance with long-term drug regimens and stated that on average about one-half of these patients are compliant. Compliance with short-term medication was extremely variable and studies were not reproducible.

It would seem reasonable to assume that errors of intake of drugs are common in the elderly patient, as they may not fully understand instructions, they often have impaired hearing or sight, they may suffer confusional states, etc. Decreased manual dexterity may lead

to difficulties in opening containers particularly the childproof type. However valid this kind of intuitive reasoning may be, objective measurements do not always support the view that the elderly are less compliant than the young. Haynes[13] reviewed studies in which associations between demographic characteristics of patients and compliance were examined. Of 37 studies reviewed only seven showed a positive association between decreased compliance and increasing age.

Failure of compliance can be difficult to detect as Caron and Roth[15] demonstrated when they found that a group of 27 physicians could not adequately assess compliance of individual patients. Questioning the patient and pill counts gives some information, but can be misleading. Measurement of blood or urine drug concentrations in suspect patients is the most direct way of assessing compliance but obviously has limited general application.

Various methods for improving compliance have been tried, among them counselling, written instructions, the use of calendars and single tablet dispensers. Most attempts to improve compliance using one or more of these techniques have reported some improvement[14] but their effects on outcome of treatment have not been adequately assessed. In general, published studies describing attempts to improve compliance do not deal specifically with the elderly. One study in the elderly[16] showed that over a 14-day period patients given tear-off calendars made fewer errors in medication than those with a tablet identification card. Both methods were better than standard verbal instruction. Despite our lack of hard evidence in this matter, commonsense suggests that the following approach may help in minimizing non-compliance:

(1) A simple regimen involving as few drugs and as few doses as possible should be prescribed. A simple explanation of the treatment should be given. A regimen containing three drugs is said to be a reasonable maximum for an old person to manage[17]. This statement is based on a subjective conclusion in one study, but it has an intuitive logic.

(2) Help in supervising a patient can be sought from a neighbour, relative or health visitor.

(3) The necessity for compliance should be emphasized and the instructions repeated at follow-up.

(4) The pharmacist should provide well-chosen easy-to-open containers, with clearly written or preferably typed instructions. The pharmacist can also emphasize the dosage instructions verbally.

PHARMACOKINETICS

Introduction

There are many changes in body composition, blood flow and physiological function (Table 3), commensurate with ageing, which may alter pharmacokinetics. In this section a number of pharmacokinetic terms are defined. This is followed by a consideration of each of the pharmacokinetic processes – absorption, distribution, metabolism and renal elimination – in relation to ageing.

Table 3 Physiological changes and ageing

Parameter	*Change*	*Reference*
Lean body mass	↓	40
Total body water	↓	41
Body fat	↑	42
Cardiac output	↓	43
Renal blood flow	↓	44
Hepatic blood flow	↓	45
Cerebral blood flow	↓	46
Renal function	↓	47
Plasma albumin concentration	↓	33

The plasma half-life of a drug ($t_{1/2}$) is the time taken for its concentration in the plasma to fall by one-half. It is usually calculated from the terminal portion of a graph of log plasma concentration versus time. The plasma half-life is a guide to the time taken to reach steady state concentration during chronic dosing and the time taken for elimination after cessation of such dosing. In each case the time is approximately four half-lives.

The degree of drug uptake by tissues relative to that in blood or plasma determines the volume of distribution (V_d). It is the apparent volume of body water into which the amount of drug in the body (A) is distributed to provide a given plasma concentration (C).

$$\text{Thus } V_d = \frac{A}{C}$$

Clearance is the volume of plasma which contains the amount of drug removed from the plasma per unit time and its units are those

of volume per unit time. The relationship of clearance to half-life and volume of distribution can be expressed as follows:

$$Cl = \frac{V_d \times 0{\cdot}693}{t_{1/2}}$$

It is apparent that a change in $t_{1/2}$ with a corresponding change in V_d need not necessarily result in a change in Cl (see section on diazepam, page 17).

During chronic dosing when a dose (D) is being administered at time intervals (T) and F is the fraction absorbed, the average steady state concentration (C_{av}) is determined by:

$$C_{av} \propto \frac{D \times F}{Cl \times T}$$

Thus Cl and F are the pharmacokinetic factors which determine average steady state concentration.

Absorption

After oral administration many factors affect drug absorption from the bowel. The disintegration time and dissolution rate of the preparation determine the rate at which the drug becomes available for absorption. These depend on drug formulation and physiochemical characteristics but in addition may be affected by age-related changes in gastrointestinal physiology. Gastric pH rises with age[18] and this may change the degree of ionization and thereby the lipid solubility of some drugs. However, the rise in gastric pH may hasten gastric emptying[19], and in some cases this tends to enhance absorption. Splanchnic blood flow[20] and small bowel mucosal surface area[21] decrease with age. These changes would tend to delay or reduce absorption.

Changes in active absorptive mechanisms appear to occur with advancing age. The absorption of galactose[22] is delayed and 3-methyl glucose absorption[23] appears to be reduced in older persons. D-xylose is also actively absorbed, but in this case absorption seems not to be impaired in the elderly[24]. Studies in animals indicate that the absorption of calcium, iron, thiamine and dextrose is diminished with increasing age[25]. However, as most drugs are passively absorbed, data pertaining to actively transported substances whether from animal or clinical studies, are of little value in predicting the possible effect of old age on absorption of drugs.

Drug absorption must be considered under two headings – rate of absorption and extent of absorption. These two parameters are not

necessarily related. The absorption rate partly determines the time to peak and the height of peak drug concentration in the plasma. Rapid absorption is important where early and high peak plasma concentrations of drug are required for clinical effect, for example with antibotics, analgesics and hypnotics. Extent of absorption is particuarly important in chronic dosing, since it is a major determinant of drug steady state plasma level and therefore of magnitude of drug effect. These two pharmacokinetic parameters, particularly extent of absorption have been little studied in the elderly.

Rate of absorption

The effect of increasing age on the rate of absorption of certain drugs is shown in Table 4. There are no age-related changes in the

Table 4 Changes in rate of absorption with advancing age

Drug	*Change*	*Reference*
Acetylsalicylic acid	→	48
Acetylsalicylic acid	→	49
Chlordiazepoxide	→ ?	50
Digoxin	↓	27
Indomethacin	→	51
Paracetamol	→	28
Phenazone	→	52
Practolol	→	53
Propicillin	→	31
Propoxyphene	→	52
Quinine	→	47
Sulphamethizole	→	28
Tetracycline	→	29

rate of absorption of most drugs studied to date. It is noteworthy that some antibiotics and a few commonly used analgesic drugs are in this group. The delay ($1{\cdot}05 \pm 0{\cdot}86$ h) in absorption of digoxin as measured by time to peak concentration (Figure 1) is probably of little clinical significance since the peak action of the drug occurs well after the absorptive phase[26].

Because of the wide scatter of values in the young a difference in the rate of absorption (absorption rate constant) of chlordiazepoxide between young and elderly groups did not quite reach statistical significance[50]. However, the data does suggest that chlordiazepoxide may be more slowly absorbed in the elderly.